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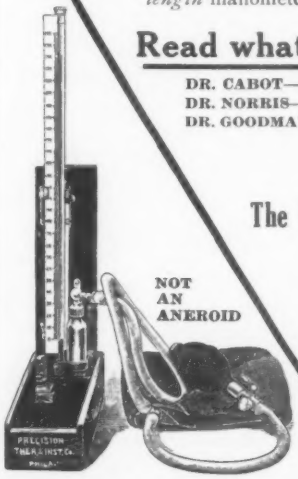

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## ORIGINAL ARTICLES

### CHEMOTHERAPY IN TUBERCULOSIS.[1]

By Paul A. Lewis, M.D.,

HENRY PHIPPS INSTITUTE OF THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

In its previous lectures on the general subject of tuberculosis the Harvey Society has been especially fortunate.

Speaking on the subject of tuberculosis in 1906, Theobald Smith said, "The present-day problems in tuberculosis which can be approached by experimental or at least by laboratory methods manifest themselves in three different ways:

"1. In the somewhat chaotic condition of opinion concerning the avenues through which tubercle bacilli gain a foothold in the body.

"2. In the wide divergence of opinion concerning the relation of bovine to human tuberculosis.

"3. In the general trend of studies toward the problem of specific immunity, with especial reference to prevention and treatment."

He presented and critically considered the evidence bearing on the portals of entry of the tubercle bacillus and laid stress on the major significance of the direct infection of the lung and associated lymph nodes by way of the inspired air.

Two years later Calmette presented a great deal of material bearing on the proposition that the tubercle bacillus gains its entry

[1] Lecture delivered before the Harvey Society of New York, November 25, 1916.

chiefly through the intestinal mucosa. Today opinion on these subjects is perhaps little less chaotic than at the time of these lectures, but the debate has largely subsided, due to a paucity of competent new evidence.

As the result of exhaustive experimental work in this country and abroad the relation between bovine and human tuberculosis may be considered to be established.

The third group of problems considered by Theobald Smith has been continuously attacked in the interim. The accomplishments of the period were summarized in able fashion by Baldwin two years ago. While immunization has so far led to no practical result in tuberculosis, we should not consider for a moment that the possibilities are exhausted. In the abstract, immunization in some form—active immunization as a preventive measure or combined passive and active immunization during the course of the disease as a therapeutic procedure—most closely simulates nature's own method. If in tuberculosis we have so far achieved no appreciable success along these lines it is doubtless that success awaits some new technical departure adapted to the exact situation, a development that may come with a fresh point of view derived from the study of some other more or less distant disease or which may more probably come as a matter of direct attack if the search is pursued with energy and in a spirit of independent inquiry.

Turning to the subject of chemotherapy in tuberculosis it should be plain that the term is used here and can only be advantageously used in the restricted sense in which it was introduced and employed by Ehrlich—not easy of concise definition—but conveying the implication of biological experimentation carefully coördinated with constructive chemical manipulation, and even, if necessary, chemical research of a most advanced type. This use of the term is emphasized because of late the word chemotherapy has become fashionable as applied to the empirical therapeutic use of any chemical substance from arsenic for gastric ulcer to zinc sulphate for dysentery; a use chiefly designed to conceal an utter absence of either thought or intelligent experimentation. Employing the term in the restricted sense I hope to do little more than to show that it may be properly employed in connection with research in tuberculosis. Even in this I can barely carry conviction as measured by any definite success in the treatment of experimental tuberculosis.

Historical considerations, on the other hand, would allow to the worker in tuberculosis, a certain proprietary freedom in the employment of this word, and especially the real conception it represents. Ehrlich once stated that he counted as most memorable the evening on which he heard Robert Koch describe to the Berlin Physiological Society his researches culminating in the discovery of the

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tubercle bacillus.[2] Koch after this discovery at once applied himself with characteristic vigor to the discovery of a disinfectant which should act to rid the body of this destructive invader. The idea of a chemical disinfection of the body was prominent in the early writings of von Behring. As Behring and Ehrlich were at this time most closely associated with Koch (it was Ehrlich who first showed how the tubercle bacillus could be easily stained), who can doubt that this idea was a dominant one and shared more or less equally by all three in those days. All were involved, each in his separate way, in the epoch-making discoveries in the realm of immunization, the theoretical development of serum therapy and its practical employment. Ehrlich alone persisted in the original idea, and finally achieved a surpassing success. This early idea then of a chemical disinfection of the body, let us examine it somewhat more closely as to what it was at its inception supposed to involve—and then see what of an essential nature had to be added to it in order to arrive at a successful result.

In Koch's writings, and in those of v. Behring of somewhat later date, it was considered possible that any disinfectant might probably act in a favorable way on bacterial infection. Many substances were examined for their disinfectant action and those found active in this sense were tried on the animal in the face of the experimental disease. Koch soon emphasized as an *a priori* consideration, the probability that a substance need not actually kill the bacteria in the body; if it would only restrain the growth of the parasite, the natural body defenses might be sufficiently aided so that cure could be attained. But even with this limitation every attempt resulted in disappointment, the stumbling-block apparently being the relatively high toxicity of the chemicals tried for the complex host as against the more limited organization of the parasite.

In a paper by Boer,[3] an assistant of Behring's in this early period, is found the germ of a most important development of this early and rather crude conception. Boer found in the course of an examination of a series of substances for their disinfectant action against a number of species of bacteria that most of them acted with a certain intensity which was of equal value against all the bacteria tried. Thus, phenol is weaker than bichloride of mercury and is weaker in the same degree no matter which microörganism is used as a test object. Methyl violet, on the contrary, was found to be seven times more active against B. anthracis than against B.

[2] "Es war in einem kleinem Raum der Physiologischen Instituts, als Koch in schlichten und klaren Worten unter Vorlegung zahlloser Präparate und Beweisstücke die Atiologie der Tuberkulose mit überzeugender Kraft darlegte. Jeder, der diesem Vortrage beigewohnt hatte, war ergriffen, und ich muss sagen, dass mir jener Abend stets also mein grösstes wissenschaftliches Erlebnis in Erinnerung geblieben ist." Ehrlich, Robert Koch, Frankfurter Zeitzung, June 2, 1910.

[3] Behring, Gesammelte Abhandlungen, Leipzig, 1893, p. 198.

diphtheria. These two bacterial species being equally susceptible to phenol, mercuric chloride and a number of other common disinfectants it is evident that in a very limited sense methyl violet is a specific disinfectant for B. anthracis.

When Ehrlich after the immunity period again turned his attention to chemical disinfectants he was naturally interested in the study of those substances exhibiting specific activities. Working with Bechold,[4 5 6] he studied a series of halogen derivatives of phenol and naphthol from this point of view. Very striking instances of this "partial specificity" as they designated it were uncovered. Without going into detail, it was shown that rather trivial chemical modifications, could profoundly alter the specific features of disinfectant action. Similar series of closely related chemical compounds have since been studied from the same viewpoint by Jacobs, Heidelberger, Amoss and Bull, at the Rockefeller Institute.

At present work of this nature is somewhat in discredit because of the profound disappointment which has resulted from most attempts to apply substances showing exquisite action in the test-tube to the more complicated situation they face when exposed in the animal body. I believe that such discouragement is premature. We are forced to admit now that which we must have foreseen, that test-tube action and *in vivo* disinfection do not go hand in hand. But of all the guides available to the intimate relation of chemical agent to parasite the study of the specific qualities of disinfectant action is the most logical, and I venture to predict that in due time in some quarter an important success will be credited to the application of this fundamental conception. In fact, if we may accept the report of Schiemann[7] such success has already been achieved in its essentials. It is stated by this observer that salvarsan, showing limited curative properties against experimental infections with the anthrax bacillus and the bacillus of swine erysipelas, has definite specific disinfectant action against these bacteria as contrasted with other species whose infections are not therapeutically influenced.

Let us leave for the moment this question of the application of *in vitro* disinfectants to the problem and turn to the first actual success achieved by Ehrlich in the treatment of an experimental infection. The benzidin dye trypan red was found capable of curing trypanosomatous infection in mice. Trypan red has very little if any action in shortening the life of the trypanosomata when the exposure is made in the test-tube. It therefore became apparent that success in this field could be achieved by leaving aside the

[4] Ztschr. f. Phys. Chemie, 1906, xlvii, 173.
[5] Ztschr. f. Hyg., 1909, lxiv, 113.
[6] Disinfektion, Paul Ehrlich (Festschrift), Jena, 1914, p. 505.
[7] Ztschr. f. Immunitatsforsg., 1914, xxiv, 167.

disinfectant qualities of substance *in vitro* and proceeding at once to the crucial test of the animal experiment with a wide variety of compounds.

If now we ask ourselves why those substances acting as disinfectants in a somewhat specific sense fail to rid the animal body of bacteria, while other substances, hardly disinfectants in any sense, are therapeutically active in a more or less specific way, the answer is in part obvious and involves important principles which must be kept constantly in mind in all chemotherapeutic experimentation. When substances active *in vitro* fail *in vivo* it is frequently because they are so distributed when introduced into the animal body that they fail to come in contact with the parasite at all. The substance is quickly eliminated in some cases, is quickly and completely destroyed in other cases, has in still other instances higher affinities for the constituents of the body fluids or cells than it has for the microörganism in question, affinities which may or may not be put in evidence by actual acute or chronic intoxication. When, on the other hand, apparently indifferent substances are found to be therapeutically active it is because in the chemical melting-pot of the animal body, new compounds, active and with the required distribution coefficient, are produced either from the substance itself or under its influence. These two series of qualities of substance, their capacity for specific antiparasitic action and their relation to the complexities of the animal body as evidenced by what can be found out or inferred in regard to their distribution in the body, are basic in the conception of chemotherapy.

When in any particular instance an attempt is made to elucidate these fundamental qualities, purely technical questions of decisive importance come into the foreground. Again, a consideration of Ehrlich's work shows most clearly what is required. It is apparent in the first place that only these diseases can be approached in this way in which the fundamental etiological relationships are cleared up with such results that we are left with a very precise method of experimentation involving in the animal the essential features at least of the pathology of the human disease. The trypanosomiases as studied by Ehrlich are almost ideal from this point of view. The local lesions in tissues are not prominent, the infection can be made to run a rapid and invariable course, the progress of the disease can be precisely followed from day to day by a very simple microscopic examination of the blood, and the animals of choice are small and inexpensive to purchase and maintain. If these cases are defective —and I think they are in some measure—it is in that the pathology of the experimental disease localization of the parasite in particular tissues does not occur as it frequently does in the spontaneous disease, and there is little local tissue reaction. Questions involving the distribution of the chemical agents are consequently much more simple. It is possibly because of this fact that the experi-

mental results have not been duplicated in a striking way in their practical therapeutic application to such conditions as sleeping sickness.

Finally, in the person, in the surpassing mental attainments, of Ehrlich another essential limitation to this form of experimentation was overcome. Coöperation so essential to achievement in every walk of modern life is more apt to materialize as between the various functional units of one man's mind than as between individuals. The united efforts of a trained chemist and a highly accomplished biologist were assured beyond possibility of even temporarily strained relations by the peculiar qualifications of this man of genius. The progress of chemotherapeutic research is contingent on a similar happy conjunction in the human mind and hands of accomplishments in these widely separated fields of research. Whether the limitation which the subject faces in consequence will in the future be surmounted by activity of individuals trained in selected parts of both fields or by the mutual and coöperative activity of specialists in the separate sciences can only be left to the chances of the future.

Having so far considered the place of chemotherapy as related to the various other possibilities of research in tuberculosis, I turn to the immediate subject of the hour. I wish very briefly to consider the facts of experimental tuberculosis in order to show what are its disadvantages and its advantages as a basis for chemotherapeutic study.

The tubercle bacillus as cultivated in the laboratory occurs in three types showing constant qualities: the human, the bovine, and the avian. With the latter we are not now concerned. With either the human or the bovine type, most warm-blooded animals, all those certainly that are commonly used in the laboratory, may be infected and the infection will run a regular course, terminating in death in many instances. The experimental disease certainly involves the essential features of the human disease. At first sight, then, the requisite conditions underlying therapeutic experimentation are already at hand. I say at first sight because, in the minds of the general medical public and those laboratory workers whose experience with tuberculosis is casual, relative certainty of result speaking generally, has been exalted to an almost mythical conception of absolute certainty in each particular case, a fundamental misconception responsible for disappointing mistakes and perhaps actual harm.

Any single culture of the tubercle bacillus is a relatively constant quantity; but, as in all other species of pathogenic bacteria, individual cultures differ in particulars which are of critical value when they are to be used for advanced experimentation. Attempts to modify the properties of particular cultures in any given or constant direction as a matter of controlled experiment have for the most

part failed, yet over periods of years and due to conditions accidentally arising a culture may profoundly change its qualities. Thus, Krause has recently conducted certain experiments which depended upon his possession in the laboratories at Saranac Lake of cultures showing constant differences in virulence, particularly one which now produces in guinea-pigs a disease which progresses for a period and then tends to heal spontaneously. With any given culture at a given time the amount inoculated and the manner in which the inoculation is made are of decisive importance to the result. With a certain culture of human type in a recent experiment of my own, $\frac{1}{10}$ mg. was inoculated intraperitonially into 15 guinea-pigs. The first of these died in eighteen days, the fourteenth died on the thirty-sixth day, and the last one lingered until the sixty-fifth day. In a subsequent experiment 14 guinea-pigs were inoculated in the same way with one-half the amount of the same culture ($\frac{1}{20}$ mg.). Of these the first died on the twentieth day; 8 were alive on the fortieth day; 4 remained on the sixtieth day; 2 still live on the nintieth day. If the amount of this culture inoculated were still further reduced we would doubtless come to a point when some animals would die and some would live for an indefinite time or perhaps recover entirely from the disease. By inoculating larger doses of this culture no doubt it would be possible to arrange an experiment in which all of the animals would be dead by the end of four weeks.

These results, conversely stated, emphasize the fact that with the same amount of culture inoculated in the same way there is a great variation in the length of time the animals may be expected to survive. With guinea-pigs I have yet to conduct such an experiment in which the last animal did not live at least twice as long as the first to die, and often the difference is much greater than this. If the inoculation is made subcutaneously this variation is increased. If it is made intravenously in guinea-pigs it is apparently not greatly, if at all, diminished. By attention to the weight and age of the animals the variability in result as to individuals is kept at a minimum, but it is always a large factor. These facts make it plain that any experiment designed to test the therapeutic activity of a substance must be so arranged as to permit of statistical interpretation finally. The probable individual variation must be completely accounted for in each experiment. This means that a considerable number of animals must be used for each substance brought under consideration and at least as many for the requisite checks. Just how large this unit group should be has probably not been satisfactorily determined even yet.

You will have noted that the actual time involved is considerable. Thirty days is no short period and ninety days is one-third of the conventional laboratory year. Contrast this with the four days of the typical animal experiment in Ehrlich's work with trypanosomata

and it is self-evident that we have here a very distinct handicap on the application of the chemotherapeutic idea to tuberculosis work.

Efforts have been repeatedly made to discount in whole or in part the variation in the length of time animals live after such inoculations by terminating the experiment on a certain date through slaughter and postmortem examination. Postmortem examination of the animals dying spontaneously reveals a variation in the exact condition of the organs which is fully as great and in my opinion considerably greater than that shown in the length of life in days. One animal dies because the liver is completely degenerated, another because the lungs are consolidated, a third is drowned in his own fluids, showing more or less local disease widely distributed, an intense edema of the lungs and the pleural cavities completely filled with fluid exudate. These conditions, if they are to be interpreted, must also be considered statistically, and this if it is to be done must involve an even larger material than when the resistance of the animal is accounted for as a single factor. Such attempts at a short cut on any scale so far attempted are quite unsound. In any experiment, after all of a sufficient group of controls are dead and accounted for, not before then, a considerable amount of guidance may in the future be obtained from the condition of the organs of killed or dying animals.

Similarly, reliance has been placed on the presence or absence of large numbers of tubercle bacilli in the lesions or apparently healthy tissues of animals dying within the period of life of controls. If an animal dying in this period shows few lesions or none, and if tubercle bacilli are found only in small numbers, it may sometimes be safe to conclude that death was not due to tuberculosis and the animal can properly be excluded from consideration. But in the presence of moderately extensive lesions it must be assumed that an animal may be as apt to die from the consequences of a largely successful effort to remove bacilli, as from the presence of the microörganism *per se*. After the last control has died the presence or absence of bacilli may have great significance in the experiment. Previous to that time, at least until much more extensive observations as to the variability of this factor have been made, opinion based on this point has no value.

Two things then, the absolute time involved in each experiment and the size of the experiment, as conditioned by the number of animals which must be used to cover individual variations, are the essential factors of difficulty that stand in the way of the application of the principles previously considered to tuberculosis as an experimental disease. Can the difficulties so imposed be directly overcome? As abstractions, very easily; as a practical matter it may easily involve a concentration of trained effort and an expenditure of money beyond that so far applied to the study of any single problem in medical science to assure an even chance of success.

It has seemed to me quite possible that the issue presented might be treated by avoiding it. I have spent a considerable amount of time in the study of various forms of local tuberculosis and of general tuberculosis in animals other than the usual guinea-pigs and rabbits, in the hope of encountering a form of the disease which would be less variable or run a shorter course than I have indicated. Most hopeful for a time seemed the study of a tuberculosis of the cornea in rabbits. With Dr. Montgomery I studied rather more in detail this interesting local disease than had previously been done. On a small scale it seemed ideal for our purpose. When, however, the test came to be made more largely it was found that the individual variation in reaction was as great as in other forms of experiment and that certain other factors were introduced which added to the difficulty. We were dealing here with an open lesion, and this very frequently became infected with extraneous organisms. Moreover, there is a constant discharge of bacilli from the purulent conjunctival sac, and unless the experiments can be segregated, the animals being cared for by already tuberculous persons, there is the constant likelihood of complicating other experiments in progress and a continuous menace to the health of one's employees. The possibilities of similar studies of other lesions or of the disease in other animals are not at all exhausted and such efforts should prove profitable in the future.

Offsetting the disadvantages which have been pointed out as inherent, tuberculosis offers an interesting opportunity quite peculiar to itself. The multiplication of the bacillus in typical instances is accompanied by a local rearrangement of the body cells to form nodular lesions readily visible to the naked eye and of characteristic structure microscopically. These nodules, the tubercles, can be used as a guide in the study of the distribution of extraneous chemical compounds to the neighborhood at least of the bacteria. The tubercles, if necessary, can be picked out and examined chemically, or more practically, for a beginning, colored substances can be chosen as the starting-point of combined chemical and biological research. These can, under favorable circumstances, be immediately recognized in the tissues, and questions of distribution can be rapidly answered by their use.

On the occasion of a visit to Baltimore four years ago I was shown some very beautiful preparations by Dr. Winternitz, preparations made in a study of the origin of the cells taking part in the reaction of the earliest hours after an infection of the animal with tubercle bacilli, and since carefully described by Bowman, Winternitz, and Evans.[8] My interest was aroused in the possibility of making a wider application of the so-called vital stains, and I shortly found by experiment that the fibrocaseous tubercle took up certain of

[8] Centralbl. f. Bkt., 1912, I Orig., lxv, 403.

these stains in a characteristic way. The results of these early experiments were recorded and summarized in the following terms:

"The first of these experiments shows again the selective action of Isaminblau for the large mononuclear phagocytic cell as pointed out by Goldman. These cells are found abundantly in the peripheral portions of fibroid tubercles.

"The second experiment is of great interest, showing, as it does conclusively, that extraneous chemical substances of proper constitution may within a few days penetrate to the caseous centre of a tuberculous mass and become concentrated there in greater degree than in the normal surrounding tissues. The particular substance used in this experiment, trypanroth, may probably be without effect on the lesion itself, but the result should be a great stimulus to the future work in a similar direction."[9]

These experiments seemed to me to be of the utmost importance as a basis for further experimental work of a coördinated chemical and biological nature. The opinion had been quite generally expressed that as the tuberculous tissue was without internal blood supply it could be reached only with difficulty if at all by medicinal agents which might be made to circulate in the blood stream. Such an opinion, if to decisive weight, would make it appear to be an unreasonable waste to experiment largely with the idea of developing general medicines which might be hoped to influence the local tuberculous process. The actual result, on the contrary, rendered such experimentation reasonable, and, as it seemed to us, eminently desirable.

DeWitt[10] in this country and v. Linden[11] abroad reported somewhat later on similar observations made independently with methylene blue. DeWitt confirmed my particular observations, reported on a number of dyes which failed to appear in the tubercle, and added trypan blue to the list of penetrating substances. I have since found, in the course of observations, so far unpublished for the most part, that a considerable number of azo dyes related in their chemical constitution to trypan red and trypan blue penetrate the tubercle in this way. DeWitt has since used methylene blue as the starting-point for a series of studies intended to serve the same purpose as those I am about to consider.

These observations served as the starting-point of a series of researches in our laboratory which are being continued at the present time with the object of finding or building up substances which shall have this penetrating quality well developed, and which shall at the same time be possessed of physiological activity of such nature that they might be expected to act favorably on the tuberculous process. If this effort should result in any measure of success the

[9] Arch. Int. Med., 1912, x, 68.
[10] Jour. Infect. Dis., 1913, xii, 68.
[11] Beitrage z. Klinik d. Tuberkulose, 1915, xxxiv, 1.

credit would be shared by me with Mr. Robert B. Krauss, who has been continuously associated with me for four years, and who has been responsible for all of the purely chemical work carried out.

The first concrete problem outlined on the basis of the considerations above outlined was to take the dye trypanroth, which had been used in the more striking of the experiments commented on, and try by chemical manipulation to form from it, or with it, a substance having physiological activity while preserving the qualities which enabled the dye to penetrate the tubercle.

Mr. Krauss undertook to make as many modifications of trypan red as he could, following certain general lines.

1. The staining qualities of the substances were to be at least in part preserved.

2. The preference was to be given to substances containing iodin, phenolic substances, or certain other constituents.

These specifications were drawn up on very general grounds, some of which may be stated as follows: Iodin was selected because of the long-standing belief among medical men that iodin was of some favorable influence on the progress of tuberculosis when applied locally either as an element or as iodoform; carbolic acid, guaiacol, and other phenolic substances were known to be relatively active disinfectants against the tubercle bacillus, and some of them also enjoyed a reputation as medicines for this disease. The staining qualities were to be preserved as far as possible as a guide to the localization in the course of the subsequent animal experimentation.

The chemical work involved was successful. In the course of a year and a half about seventy-five compounds were secured on the plan outlined. The chemical manipulations and results were published by Krauss.[12] These preparations were used in a preliminary way in animal experiments and some interesting observations were made. In general it was indicated that none of the substances exerted any curative influence on experimental tuberculosis. Some of them seemed, however, to have a definite influence on the vigor and rate of the formation of bloodvessels and connective tissue in and around the tuberculous process, the tests being made on the rabbit cornea.

The plan had been to prepare enough of each substance for a moderate amount of preliminary experimentation and then to make again those which seemed useful for further work. About the time the preliminary study of these compounds was completed the war arose and necessitated a change of plan. We had been purchasing trypan red from abroad and further regular supply was cut off. What was on hand and the occasional lots since secured we have used in a study, so far uncompleted, of the composition of the substance with view to its manufacture.

[12] Jour. Am. Chem. Soc., 1914, xxxvi, 961.

I have already said that following our observation that the tuberculous tissue in the living animal was easily penetrated by trypan red, many other dyes of the same general class, chemically speaking, were tested for their reaction in this particular. A considerable number were found which could become concentrated in the diseased tissue to a greater or less extent. Many of these had never been accurately described from a chemical point of view, others presented difficulty of manufacture beyond our means. After much consideration a dye known to the trade as Niagara blue 2B (benzidin + 2H acid) was chosen as the starting-point of a second attempt to construct a series of iodin and phenol compounds. It has been necessary, owing to the state of the market, for us to build up this substance from the raw products. This has been accomplished and a considerable series of compounds made by adding iodin and phenolic substances to Niagara blue have been studied, with rather meager results, which I shall not comment on now.

Covering about the same period of time as these studies on the relation of the vital stains to the diseased tissue, and in the hope of acquiring information which should in some measure guide that work, we have been studying the disinfectant action of various substances for the tubercle bacillus. We have hoped to uncover substances having the partially specific action discussed in the earlier paragraphs of this paper. Much time has been spent over methods. The procedure by which the results here considered were obtained was to determine the least concentration of the substance in glycerin-boullion, which would definitely inhibit the growth of the tubercle bacillus.

Because of the relation to the work outlined in considering the subject of the vital stains, we have so far paid particular attention to anilin dyes. We have also considered the more common disinfectants and some substances which are used in the building-up dyes. In order to get an idea of the specific qualities of the inhibiting action of the substances tested the typhoid bacillus was at first used in comparison with the tubercle bacillus. Very recently in the course of some work being carried out for the Pneumonia Commission of the city of Philadelphia I have gone over the whole field again, using the pneumococcus and staphylococcus aureus. Several hundred substances have in this way been examined with the following general results:

I. The growth of the typhoid bacillus is, with few exceptions, if any, less readily inhibited by anilin dyes than that of the pneumococcus, staphylococcus aureus, or the tubercle bacillus.

II. The triphenylmethane dyes, as a group, inhibit the growth of the pneumococcus and staphylococcus in dilutions which do not inhibit the tubercle bacillus. Among themselves these dyes vary greatly in the concentrations at which the four species are affected, both absolutely and relatively.

III. The azo dyes as a group inhibit the growth of the tubercle bacillus more readily than that of either pneumococcus or staphylococcus aureus. Again, there is a great relative and absolute variation in the effective concentrations. In the extreme instances in this group the tubercle bacillus is one or two hundred times as susceptible as the pneumococcus, and it seems proper to consider that the inhibitory power is in large measure specific.

IV. The other great groups of dyes give less striking results, the oxazines and thiazines, to which methylene blue belongs, are more active against the cocci; the eurhodines, with neutral red as an example, are more effective against the tubercle bacillus.

Certain other points developed by this work deserve passing mention. Many dyes, the majority perhaps, stain the growing membrane of the tubercle bacillus with greater or less intensity. The inhibitory power of the dyes is not at all, however, a function of this capacity to stain the membrane, nor is it a function of any particular staining quality of the dyes for silk, wool, or cotton, so far as we have been able to determine up to the present; nor of the solubility of the dye in alcohol or oil as compared to water. A small amount of work so far carried out indicates that among organic compounds other than the dyes, substances exist showing the same variable capacity to restrain the growth of the tubercle bacillus. Also a very limited number of experiments indicate that this capacity to restrain growth is not directly related according to any uniform or simple rule to the true disinfectant or lethal action of substances. Much more work will be required before these observations can be interpreted in terms of previous work with disinfectants.

Thus, approaching our problem from one point of view we have found a number of substances capable of penetrating tuberculous tissue and consequently having, as it seems to us, at least a slightly better chance of acting as antibacterial agents in tuberculosis than those which cannot so penetrate the diseased tissue. From another point of view we have found many substances possessing in marked degree and in a partially specific way the ability to greatly restrain the growth of the tubercle bacillus in the very limited conditions of the test-tube.

It has for some time back been a matter of serious effort with us to bring these two sets of qualities together in the same substance. We have had a definite though limited success in this effort. The dye Niagara blue 2B can be made to enter into chemical combination with various substances, iodin, phenol, certain fatty acids, and the like. The resulting products are apparently definite chemical compounds. As a rule they are dyes and with properties noticeably different in one or more particulars from the original substance. As a general thing the inhibitory capacity against the cultures is distinctly increased; the capacity to enter the tuberculous tissue is, on the contrary, usually lost entirely or greatly

diminished. In one instance so far a condensation product of Niagara blue with formic acid, the partially specific inhibitory value, is raised about twenty times, from $\frac{1}{5000}$ to $\frac{1}{100000}$ the staining qualities for tuberculous tissues being in large measure retained.

Again, in studying the inhibitory power of various dyes, Mr. Krauss has constructed a long series of compounds, not new in principle, but for the most part never before made, according to the following scheme: Benzidin monosulphonic acid is so treated as to diazotize its free $NH_2$ groups. There is then added under proper conditions a quantity of the variant substance calculated to react completely with one of the $NH_2$ groups. When the reaction is complete there is added sufficient amidonaphtholdisulphonic acid (H) to react completely with the other $NH_2$ group. In this series we have also encountered a number of dyes possessing distinct inhibitory powers. Very few members of the series, so far as it has yet been extended, have any staining qualities as applied to the tissues of the living animal. When crude creosote is used as the critical component, however, a mixture of closely related dyes is produced in which both qualities are present in marked degree. These products are violet-blue dyes, staining the connective tissues of the living animal with moderate intensity and penetrating the tubercles very well. The inhibitory power of the mixture is stated in our terminology at 100000 or about one hundred times that of the dyes trypan red and trypan blue, which were the starting-point of our work in this direction. Partial specificity is also manifested by this preparation.

The accomplishments of our laboratory up to the present in the endeavor to study tuberculosis from the chemotherapeutic point of view can then be summarized in a sentence: we have built up several substances which in the test-tube are capable of restraining the growth of the tubercle bacillus in marked and measureably specific degree, and which when injected into the living tuberculous animal are capable of penetrating to the centre of the masses of diseased tissue.

Attractive as may be the plan by which these substances have been reached it would still be only the happiest accident if their further qualities were such as to render them active against the progress of tuberculosis in the animal body. Neither would the failure of two such substances mean that the idea is fruitless. For the present therefore our efforts in the chemical laboratory are directed toward increasing the number of substances possessing these (as it seems to us) fundamentally desirable qualities. We have also turned ourselves seriously to the testing of the possibilities of these substances and their relation as therapeutic agents. The latter phase of our work is scarcely begun and I shall pass it by with but few words.

Drawing on the literature for precedents I may cite the following studies as the most striking of the available examples:

1. Koch and his pupils in repeated experiments during the years 1890–1897 demonstrated that by the use of tuberculin the life of guinea-pigs infected with considerable amounts of pure cultures of the tubercle bacillus could be definitely prolonged. These tuberculin experiments are worthy of the most serious consideration. The same result was reported by a number of different observers at the time and I find no contradictory experiments. The exact chemical nature of tuberculin has never been determined and it is to be presumed that its action comes within the field of immunity reactions rather than that of chemotherapy. I have included this substance in this brief discussion because I believe that the results with it are the best available standard on the basis of which the value of other results may be estimated.

2. Von Linden[13] in 1912 and again in 1915 presented tables showing that by the use of compounds or mixtures containing copper; or copper and methylene blue; or copper, lecithin, and cod-liver oil as a salve, with or without the separate administration of iodized methylene blue, the life of tuberculous guinea-pigs could be prolonged. The results as presented compare favorably with those gotten earlier with tuberculin, but in no way surpass them. Attempts to repeat some of the experiments by Corper in this country failed and Selter abroad has denied their significance.

3. Certain tables published by DeWitt[14] (1914) may be interpreted as evidence that copper and mercury compounds (or salts) of trypan blue can act favorably on the progress of tuberculosis in guinea-pigs, although the author does not put forward any positive claim for them. DeWitt has since stated publicly that she had obtained more definitely favorable results with a mercury compound of methylene blue.

4. Koga[15] (1916) believes he has attained results of value with a compound containing copper and cyanogen. On the face of the evidence again, this substance produces a result comparable to tuberculin but not surpassing it.

5. In the case of the two substances whose development in our hands I have described above, the one, that made by condensing formic acid with Niagara blue, has done only harm in guinea-pig experiments so far. In this it corresponds to Niagara blue itself. The diazo creosote compound seems in preliminary experiments to be capable of extending the period of life of infected guinea-pigs in certain instances. The percentage of animals favorably affected in any series is less than in the tuberculin experiments of Koch's co-workers.

[13] Loc. cit.
[14] Jour. Infect. Dis., 1914, xiv, 498.
[15] Jour. Exp. Med., 1916, xxiv, 107.

Those critically inclined need not search far in the original accounts given of any of these experiments to find ground for denying that they are of significance. Such criticism has been offered and will certainly be continually forthcoming. Insofar as attempts have been made or are being made to introduce any of these substances into the practice of medicine, any amount of skeptical opposition is in my opinion fully warranted. In 1890 it was quite justifiable to take the first favorable results obtained in the laboratory and make careful clinical trial of tuberculin. We should, however, profit by this experience and proceed with great caution in the clinic until the evidence shows that new substances are distinctly better than tuberculin experimentally.

In the interest of scientific progress, on the other hand, all of these results should be treated with great charity. In view of the purely statistical nature of the inquiry, the experiments must be repeated a number of times before they are finally accepted as evidence, but it must be remembered that a single failure has no more interest than a single success. If it be granted as a probability that some measure of the truth may lie in these observations, the future of chemotherapeutic studies in tuberculosis is not discouraging. At this stage of development the possibilities compare favorably in this particular case with those which offered for the broader subject of chemotherapy when Ehrlich was first able to cure trypanosomatous mice with trypan red. Several substances seem now to be known which are capable of giving a slight advantage to the host in its contest with the parasite. This number must be multiplied by empirical search through known chemical compounds, and each such substance showing a suggestive lead must be subjected to carefully considered chemical manipulation to develop to the full its latent possibilities. Each year of the five that I have been actively engaged in this work has seen some added idea or suggestion of real value, and we may be sure that if in the future faith is expressed in continuous experimentation and confidence is put in evidence by financial support adequate to the size of the task in hand the desired result will be achieved.

## REFERENCES.

The following books contain matter of the first importance to anyone interested in the development of the subject of this lecture or related questions:

1. Gesammelte Werke von Robert Koch, Leipzig, 1912.
2. Behring, Gesammelte Abhandlungen, Leipzig, 1893.
3. Paul Ehrlich, Jena, 1914.

# STRANGULATED RETROPERITONEAL HERNIA INTO THE PARADUODENAL FOSSA; OPERATION; DEATH ON THE NINTH DAY.

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Retroperitoneal hernia is rarely encountered on the operating table. Up to 1899 Moynihan could find only 57 cases on record of the variety into the left duodenojejunal fossa (to which type the present case belongs), the majority of these having been accidentally found at autopsy, and occurring independently of the disease producing death. Coley[1] says only 10 successful cases of operation have been reported, 9 of left and 1 of right duodenal hernia.

It is not an uncommon occurrence to have two or more of these retroperitoneal fossæ present in the same individual, so that it is difficult to give an accurate description of their boundaries. The folds which form the boundaries are formed in the fetus by the fusion of the left surface of the primitive mesentery of the duodenum with the right surface of the descending mesocolon, and become accentuated by traction made upon this line of fusion by the eventual drifting of the duodenum to the right and of the descending mesocolon toward the left. The fossa which became the seat of hernia in our case, and which is most frequently involved in cases of duodenojejunal hernia is known as the paraduodenal fossa or fossa of Landzert (1872). The fold producing it results from the presence of the inferior mesenteric vein, for which the fold acts as a mesentery. This vein, passing upward from the mesorectum, verges toward the midline on its way to empty into the splenic vein, and in most cases runs entirely retroperitoneally, not raising any fold or reduplication of the peritoneum. When, however, this fold, or *plica renosa* as it is called, is present, it consists of a vertical and a horizontal portion, the vertical being to the left of and below the fossa and the horizontal bounding the fossa above. Just to the left of this vein, the left colic artery is found, running upward from its origin in the inferior mesenteric artery. The lower boundary of the fossa is completed by a serous fold, the mesentericomesocolic fold, which runs from the left side of the mesentery downward and a little laterally to the right side of the upper meso-

[1] Keen's Surgery, 1908, iv, 102.

sigmoid. To the mesial side of the paraduodenal fossa is the root of the mesentery. This paraduodenal fossa, then, is situated to the left of and some distance away from the ascending limb of the duodenum (Fig. 1). Posteriorly it is bounded by the peritoneum covering the psoas muscle, the renal vessels, the ureter, and a portion of the left kidney. Its orifice looks downward and to the right, its cavity upward and to the left. The width of its orifice depends on the distance of the inferior mesenteric vein from the duodenojejunal flexure.

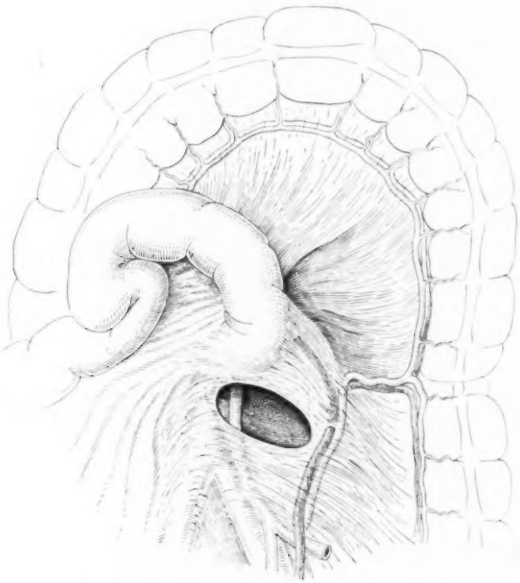

FIG. 1.—The paraduodenal fossa or the left duodeno-jejunal fossa. Note the inferior mesenteric vein and the left colic artery near the left border of the fossa. (After Poirier and Charpy.)

The causes of these herniæ are similar to those which produce other types. The presence of a deep fossa, with tense margins, and intestines which are freely movable, predisposes to the development of such a hernia. Under such circumstances a coil of intestine may be forced into the fossa by violent peristalsis or by the sudden increase of intra-abdominal pressure which follows crying in infancy or sudden strains in adult life. The hernia may develop almost at any age. Moynihan mentions a case in a child, aged fourteen days; and in herniæ which first cause symptoms in adult life, as in our own patient, a man, aged forty-seven years, it is often impossible

to know how long the condition may have existed without causing any symptoms.

In most cases the previous history is negative, though, as in the present case, there may have been attacks of abdominal pain, generally ascribed to "indigestion." The symptoms of strangulation are merely those of intestinal obstruction, and frequently the patient is not seen until peritonitis has developed. If the patient be seen early the physical signs probably are more reliable than the symptoms. While the size of these herniæ varies considerably, they usually are of sufficient size to produce a circumscribed globular fulness which, when small, is located slightly above and to the left of the umbilicus. When they attain their maximum size, however, they may occupy one-third of the abdominal cavity. The prominence formed by the hernia is then especially noticeable in contrast to the flatter area to the right, occupied by the ascending and transverse colon and by the few remaining coils of small intestine not involved in the hernial sac. In this respect they may resemble those cases of intussusception which present Dance's sign. Sometimes, as the hernia increases in size, it may be discovered on palpation, or borborygmi and subjective symptoms may point to the region of the abdomen involved. To palpation, the mass may have either a doughy or a cystic feel, but no wave of fluctuation can be obtained. The statement made by Moynihan that the tumor always yields a sonorous note on percussion and clear intestinal sounds on auscultation, no doubt may be true in nearly all cases seen early, particularly when no strangulation is present; but in our own patient all intestinal sounds were absent, owing to beginning peritonitis; and the percussion note was dull, which may be explained by the presence of free fluid outside of the hernial sac and by the accumulation inside the intestines within the sac of three enemas which had not been expelled.

Other physical signs which are said to occur are the presence of hemorrhoids from obstruction of the inferior mesenteric vein in the neck of the sac, and also a dilatation of the superficial abdominal veins serving as anastomosis between the epigastric and mammary.

On opening the abdomen a large globular mass is seen, situated to the left of the lumbar vertebræ. This mass is neither cystic nor hard and nodular, but is doughy in consistency, and the coils of intestine can be palpated beneath the smooth peritoneal covering of the sac. The colon retains its normal relationships, with the exception of the descending portion, which is pushed far to the left side. The entire small intestine may be within the hernial sac, in which case the only coil emerging from the sac is that nearest the cecum. Some cases have shown coils of small intestine to enter and to leave the sac, thence to reënter and again to leave it. The case herewith reported showed a few coils of upper jejunum lying outside the sac, while the duodenojejunal flexure itself, and all

the rest of the jejunum and the ileum, to within a few inches of the cecum, formed the contents of the hernial sac. The loops of intestine lying outside the sac, if there be obstruction, as in our own case, will be much distended; and after strangulation has existed for a number of hours, free abdominal fluid will be present.

The most plausible explanation for the enormous size of some of these herniæ is that the lower portion of the gut is the first to enter the sac, and that the remainder of the intestinal tube is carried into the sac by peristalsis, just as in an intussusception the intussusceptum is carried into the intussuscipiens. If the orifice of the sac be large, and if peristalsis be violent, portions of the interned gut may be forced out from time to time; or perhaps several widely separated loops of intestine may be involved from the beginning. Either of these factors would explain the condition in which portions of gut are seen to enter, leave, and again enter the sac. It, therefore follows that in reducing these herniæ at operation, traction should be made on the highest portion of gut involved, as it will be found this has been the last to enter. It also follows that the lowest portion of bowel involved is most apt to be the seat of strangulation; although this may arise at any part from the presence of adhesions or kinks, or from constriction at the orifice of the sac.

The enormous size of some of these herniæ has already been mentioned. Cases measuring as little as 1.5 x 2.5 cm. are on record, while others have been reported measuring 14.5 x 24.5 cm., the larger measurement being in the longitudinal axis of the body. In the present case no accurate measurement was possible; but it is sufficient to say that the sac appeared the size of a football, and filled about one-third of the entire abdominal cavity. These herniæ spread upward into the transverse mesocolon, outward toward the descending mesocolon, or outward and downward, as in the present case.

The sac may be described as a pocket in the peritoneum. It consists of a single layer of peritoneum in itself: The posterior surface rests upon the retroperitoneal structures while the anterior layer lies in contact with the posterior surface of the posterior parietal peritoneum, giving us two peritoneal layers anterior to the contents of the sac. The orifice of the sac, like the hernial mass, varies greatly in size. In the recorded cases the breadth has measured from 3.5 to 6.5 cm. and the length from 1.5 to 13 cm. In our case the diameter of the orifice was about 5 cm.; after incision of the constricting margin it was easy to introduce the entire hand into the sac.

In the treatment of these herniæ it is especially important to bear in mind the structures which run in the anterior wall of the sac, at or near its free margin, namely, the inferior mesenteric vein and the left colic artery. It is often necessary to relieve the strangulation before the hernia can be reduced; and when the vein lies close to the

orifice the only place at which an incision can be safely made is at the lower border of the constriction through the mesenterico-mesocolic fold, keeping to the mesial side of the vein. In all cases careful palpation should be made for the location of these vessels and injury to them avoided. After relief of the strangulation the hernia should be reduced as described above, beginning with the uppermost loop of intestine. After reduction the intestines are to be treated as in other cases of strangulated hernia. Finally attention must be paid to the retroperitoneal sac, which will predispose to a recurrence of the hernia if nothing is done to prevent such a sequel. The simplest method of disposing of the sac is to close its orifice by sutures, sewing the free anterior margin to the posterior parietal peritoneum which covers the psoas muscle, etc. This is what was done in our case, owing to the poor condition of the patient. There are, however, two objections to this procedure; the first was shown in our case at autopsy ten days after operation, when the suture of chromic catgut was beginning to be absorbed, and the two peritoneal surfaces had not become tightly adherent, thus opening a way for a recurrence of the hernia. The second objection is the danger of cyst formation in this walled-off sac. The operation of choice, therefore, though only applicable when the patient's condition warrants a rather prolonged operation, is to excise the entire sac and then to suture the remaining two edges of peritoneum. In either operation the inferior mesenteric vein is constantly in danger of injury. And though its division and ligation, or even a similar treatment of the ascending branch of the left colic artery, might not entail a fatal result, injury to either would subject the patient to much risk, and considerably complicate the operation.

Case History. Arthur C., aged forty-seven years, a laborer by occupation, was admitted to Dr. Frazier's service in the Episcopal Hospital, Philadelphia, September 25, 1915; discharged October 6, 1915 (died).

*Family History.* Negative.

*Previous History.* For years the man has had attacks of cramp-like pain in the upper abdomen. One especially severe attack occurred about eight years ago, but he recovered without operation. These attacks seem to occur more frequently after eating steak or crabmeat. Vomiting occurs and is followed by relief of the pain. The bowels are not constipated during these attacks, but move regularly once daily. Between these attacks the patient had been troubled at times by morning gagging; he does not know what causes this, but admits that in addition to the use of tobacco and the milder beverages, such as tea and coffee, he has always been a heavy drinker of beer. He has done heavy laboring work all his life.

*Present Illness.* The chief complaint is intense abdominal pain. The present condition began about sixteen hours previous to admis-

sion, with severe cramp-like pain in the upper abdomen. This came on him suddenly while at work, about 8 o'clock in the morning, and has continued without relief. The pain has remained generalized over the upper abdomen. Shortly after the onset of the pain he vomited a small amount of clear fluid. Vomiting has been repeated seven or eight times, and on the last occasion the vomitus was dark in color. Before admission to the hospital he was given three enemas by his physician; none of these were expelled. On admission he said his pain was somewhat relieved.

*Physical Examination.* The patient is well nourished and does not appear older than his given age. Inspection of the eyes shows a bilateral coloboma, which he states is congenital. Aside from this abnormality, the face, head, and neck are negative, as is the heart. Auscultation over the lungs, however, reveals an occasional rale at each base on deep inspiration. The abdomen is symmetrically distended; its walls are muscular, and there is no dilatation of the superficial veins. There is marked generalized rigidity, making palpation of the various organs or abnormal masses impossible. Palpation is painful over the entire abdomen, but especially marked above and to the left of the umbilicus. There is a peculiar doughy or cystic sensation to the palpating hand, different from that usually obtained in cases of peritonitis. On percussion the note seems unusually dull for gaseous distention, but no fluid wave can be obtained. The liver dulness appears to be about normal, though it cannot be accurately outlined. There is entire absence of peristaltic sounds. Examination of the extremities and external genitalia was negative. The white-blood cells numbered 18,000.

The patient was admitted to the hospital at midnight and refused to have any operation done. His vomiting continued, and by the following morning the vomitus was quite dark in color and was beginning to have a fecal odor. A second blood count showed 17,680 white-blood cells, with 88 per cent. polymorphonuclears.

*Operation.* Between 1 and 2 o'clock in the afternoon of the day after admission, and thirty hours after the onset of his acute condition, the patient finally gave his consent for operation, which was immediately performed. At this time the abdomen was immensely distended and tense; there was dulness all over, except under the left lower ribs, the tympany here being due to the stomach. There was great tenderness everywhere. No peristalsis was audible. No definite diagnosis was made,[2] but it was noted that "if this is peritonitis, there must be a quantity of pus under tension."

Nitrous oxide and ether were used for anesthesia, both of which were taken poorly. A right rectus (paramedian) incision was made in the epigastric and umbilical regions, the incision being enlarged subsequently to a length of 17 cm. (7 inches). Bloody serum

[2] The diagnosis on admission was "perforated duodenal ulcer."

poured out on opening the peritoneal cavity. (No growth was obtained from its culture.) A few coils of obstructed small intestine lay in the right kidney pouch, distended to 7.5 cm. in diameter, and almost black. No coils of intestine tended to protrude, and in spite of the large abdominal wound it was impossible to deliver those seen. The hand, introduced, felt a large cystic mass as large as a football in the center of the abdomen, and a few coils of collapsed intestine to the left and in the pelvis. These were evidently the

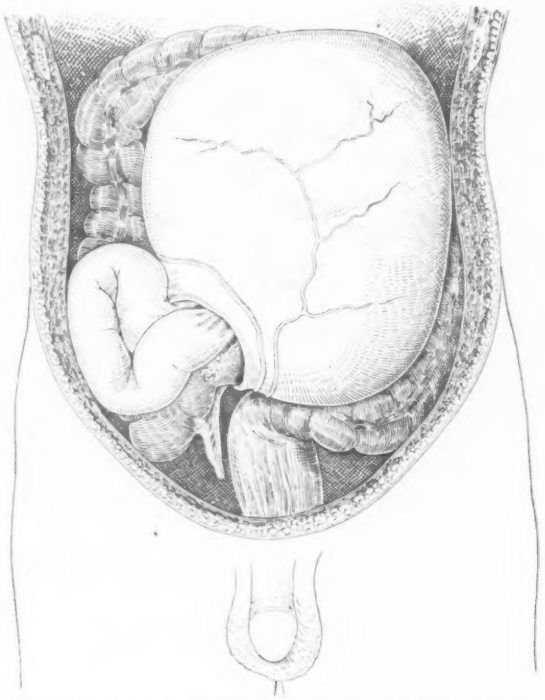

FIG. 2.—Diagram of a case of strangulated retroperitoneal hernia into the paraduodenal fossa.

descending colon and sigmoid. The liver, stomach, and pylorus could be felt in their normal positions above the mass. It was quite evident that all the small intestines, with the exception of the few obstructed coils first encountered, had entered a retroperitoneal hernia and were strangulated (Fig. 2). The entire mass was then delivered through the abdominal incision by depressing the abdominal walls around it. The orifice of the sac could now be seen, about 5 cm. in diameter, on the right side of the mass, the intestines

having entered from the right and travelled toward the left. As no important bloodvessel could be detected in the constricting ring, its anterior margin was divided for about 1 cm. The coils of intestine contained in the sac were then easily delivered, beginning at the upper end. All these coils were distended and congested, but unadherent. Their contents evidently consisted of an accumulation of intestinal juices, plus the three unexpelled enemas which had been administered to the patient before his admission to the hospital. The last coil extracted was black and looked almost gangrenous for a distance of 25 to 30 cm. This last coil was continuous, with about 4 cm. of normal intestine, which had not been within the sac, and which appeared to enter the cecum. The upper coils of small intestine which had been within the sac were almost normal, and were directly continuous with the much distended coils of small intestine seen on first entering the abdomen, and lying in the right kidney pouch. These much distended coils in turn were continuous with the duodenojejunal flexure, which lay within the orifice of the sac on its cephalad margin.

The condition of the terminal loop of ileum gave most concern. Upon application of hot saline solution the normal color was partially regained, with the exception of numerous small spots, where it was feared perforations might develop. An anastomosis was considered, but owing to the patient's condition, and the difficulty of finding the large bowel (which was pushed out of sight by the hernial sac), this idea was abandoned. In addition to the damaged condition of the gut itself the bloodvessels in the mesentery of several coils of intestine were thrombosed.

The hernial sac was then explored, the orifice now easily admitting the surgeon's hand. It was found to be an invagination of the posterior parietal peritoneum to the left of the origin of the jejunum, and its entire contents, with the exception of the duodenojejunal flexure (which lay in the office), had been reduced. The free anterior margin of the orifice of the sac was now sutured to the posterior parietal peritoneum, with a continuous suture of No. 2 chromicized catgut. Gauze packs were removed from the abdomen, the intestines replaced, and the abdominal wound closed, without drainage, by means of heavy mass sutures of silkworm gut, passing through all layers of the abdominal wall; the anterior sheath of the rectus muscle was sutured separately with a buried suture of No. 2 chromicized catgut.

*Postoperative History.* The progress of this case is interesting for the remarkable attempt of nature to restore the abdominal condition to normal.

On the *first day* after operation the patient retained water neither by mouth nor by bowel. He passed no flatus, but the abdomen was only slightly distended.

On the *second day* gastric lavage was necessary both morning and

evening to relieve distention and vomiting. However, 2 pints of water were retained by bowel and about 7 ounces by mouth.

On the *third day* gastric lavage was required once. Four pints of water were retained by bowel, and 10 ounces of broth totalling about 40 calories, by mouth.

On the *fourth day* gastric lavage was required once. Four pints of water and a nutritive enema containing 776 calories were retained by bowel, and 6 ounces of water and small quantities of broth and albumen, totalling about 6 calories, were retained by mouth. Beginning impairment of the percussion note at the base of the right lung was noted today.

On the *fifth day* the abdomen was softer, there was less pain, and the total quantity of vomitus was only 11 ounces. Nourishment of 1552 caloric value was retained by bowel and 18 calories by mouth. The lower third of the incision was infected. A clean-cut basal pneumonia had developed on the right.

On the *sixth day* the abdominal condition continued to improve; 1552 calories of food were taken by bowel and 85 calories by mouth. The abdominal incision was sloughing at its lower angle. Consolidation of the right base persisted and the patient was delirious at times.

On the *seventh day* the abdomen was distended and there was considerable vomiting. Rectal nourishment was discontinued and 1126 calories were given by mouth; all of this nourishment, however, was not retained. The infection of the abdominal incision did not seem to be spreading, but one silkworm-gut suture had torn out. The patient continued delirious at times.

On the *eighth day* the abdomen was softer and the patient was more comfortable. The total vomitus measured 10 ounces, while 5 pints of water and 826 calories of food were retained. The incision showed no marked change. Although the patient was still slightly delirious at times, he was less restless and the area of pulmonary consolidation seemed to be resolving.

On the *ninth day* the abdomen was soft and an alum enema was effectual. The patient retained practically all of 1159 calories of food, only slight vomiting occurring. The abdominal incision was beginning to granulate at the infected area. The mental condition was more rational and the consolidated area in the lung was becoming replaced by moist rales. Coughing was severe, and a note was made that the patient seemed to be on the verge of his crisis.

Unfortunately, toward evening, after a severe coughing spell, the patient became more restless and complained of pain in his incision. On removal of the binder and dressings it was found that about 2 feet of intestine were lying on the surface of the abdomen, the lower angle of the incision having given away. The intestinal coils were replaced under heavy doses of morphin and a few whiffs of

chloroform, and the gaping part of the incision was sutured with through-and-through silkworm-gut sutures over a large gauze sponge, one end of which was allowed to protrude from the lower angle of the incision. Eight hours later the patient died.

It was impossible to obtain permission for an autopsy, but exploration of the abdomen through the operative incision showed that there was no active peritonitis. The sutures obliterating the orifice of the hernial sac were beginning to be absorbed, but very little agglutination of the approximated serous surfaces had occurred, so whether the end result would have been a complete closure of this opening it is impossible to say.

We mentioned in the description of the operation that the free margin of the hernial orifice contained no important structures and that it was incised for about 1 cm. in order to relieve the strangulation. More careful examination, postmortem, however, showed that the inferior mesenteric vein ran less than 2.5 cm. from the free margin, and that only a little further distant was the left colic artery, either of which might have been wounded had the incision been carried farther.

Examination of the intestines showed what wonderful attempts nature makes to restore a damaged organ to normal. Much of the gut had regained its normal color, while those spots which we described as gangrenous had doubled up on themselves and their healthy edges had become adherent, thereby inverting the damaged area more perfectly than the surgeon himself could have done. This occurred in two instances, while a third threatening perforation was protected by adherent omentum.

## THE MINERAL METABOLISM OF EXPERIMENTAL SCURVY OF THE GUINEA-PIG.

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and

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I. Historical. A glance at the literature of scurvy since our publication[1] early in 1912 shows the great interest manifested by many in the so-called deficiency diseases. Theodor Fröhlich and Valentine Fürst,[2 3 4] in 1912, reported further studies upon

[1] L. Baumann and C. P. Howard: Arch. Int. Med., 1912, ix, 665.
[2] Ztschr. f. Hyg. u. Infectionskrankh., 1912, lxxii, 1.
[3] Ibid., p. 72.
[4] Ibid., p. 155.

experimental scurvy in a series of 96 guinea-pigs. The disease could be produced with almost mathematical certainty when guinea-pigs were fed on an exclusive diet of oats or other grains. In the course of twenty-eight to thirty days the animals failed and died. Postmortem there was found loosening of the back teeth, hyperemia of the gums, and, microscopically, hemorrhages into the muscles about the joints of the extremities, extravasations about the costo-chondral joints, and frequently epiphysolitis about the upper end of the tibia. Further, the histological changes in the epiphyses and in the bone marrow were identical with those seen in infantile scurvy. They saw similar changes in dogs fed on oatmeal and beef fat and in hogs fed with rye bread, to which boiled beef and rice and dry boiled fish were sometimes added.

Feeding with cabbage, carrots, or dandelions exclusively do not produce such changes, though there may be considerable loss of weight, so that they believe inanition is not the cause of the symptom-complex. Further, they found that various vegetables prevent the development of scurvy or influence its course if present. Boiling or prolonged drying of these vegetables reduces or destroys the antiscorbutic effect. Scurvy-producing foods can be changed to antiscorbutic foods by allowing them to sprout.

They believe that the absence of one or more unknown substances is responsible for the disease and that there is a series of antiscorbutic substances with various properties, but with a common nucleus, which is the true antiscorbutic agent.

They failed to produce scurvy in guinea-pigs by feeding with heated milk unless it were heated to a higher temperature than that used in infant feeding. They could offer no explanation for this difference in the reaction to milk, while the child and guinea-pig react identically to cereals. However, while milk heated to 100° C. does not produce scurvy it does lose its antiscorbutic property. In their last contribution[5] on the preservation and extraction of the specific substance of antiscorbutic foods they point out that dandelion leaves and carrots when dried at 37° C. lose to a marked extent or entirely their antiscorbutic properties. Cabbage juice, which prevents the disease, when heated to 60° to 70° C. has no antiscorbutic effect. The antiscorbutic substances in lime juice and lemon juice are thermostable and the alkaline extract of cabbage and dandelion become almost thermostable when acidified. Hot alcohol (80 per cent.) containing citric acid (1 per cent.) can extract and bring into solution the antiscorbutic substances of freshly dried cabbage. Concerning the exact nature of this substance they are not yet able to speak. It may be of the nature of an enzyme on account of the small amount necessary to prevent scurvy and its thermolability.

[5] A. Holst u. T. Frölich: Ibid., 1913, lxxv, 334.

This experimental production of scurvy by the Scandinavian writers has been confirmed by many, including Kohlbrugge,[6] Hart, Talbot, etc.

Carl Hart[7] produced characteristic bone changes in guinea-pigs when fed on milk alone. The degeneration of the lymphoid marrow into a less vascular, mucoid, or fibrous tissue, together with an impoverization of the osseous tissue at the epidiaphyseal region of the long bones and the persistence of the preparatory calcifying zone with infraction and fractures are the phenomena noted.

Talbot, Dodd, and Peterson[8] emphasized the value in the roentgenogram of the definite "white line" of Fraenkel[9] at the junction of the epiphysis with the diaphysis, which occurs before the subperiosteal hemorrhages and other cardinal symptoms are evident. They confirmed Holst in the production of scurvy in guinea-pigs, in one of which a definite white line could be seen.

F. Lust and L. Klocmann[10] have studied the metabolism in a case of infantile scurvy and found at the height of the disease a slightly abnormal calcium retention. After a month's treatment there was a marked calcium loss, while during the period of convalescence a calcium equilibrium had almost been established. This is in decided contrast to rickets. They conclude there is no evidence that a lack of minerals is a primary or secondary factor in the etiology of the disease.

Schmorl[11] produced in dogs by means of a phosphorus-poor diet a disease that showed great likeness to Barlow's disease but which could not be identified with it. Thus, one animal passed bloody stools, developed convulsions, and died one month after the diet was instituted; another showed difficulty in walking and died in two months. Postmortem there were no hemorrhages and the teeth were normal. The bones of the thorax and extremities showed porosity of the compact layer and diminution of the spongiosa at the epiphyseal ends. The lymphoid marrow was usually replaced by fibrous tissue, with a few spindle and typical marrow cells, a picture resembling that seen in Barlow's disease, except for the infrequency of the hemorrhages. Further, the cartilage proliferation zone was broadened and the calcification zone defective; there were no subperiosteal hemorrhages. The small amount of osseous tissue is due to the diminished function of the osteoblasts and the increased bone destruction. The cartilage itself is not affected but the conversion of cartilage into bone is delayed.

[6] Centralbl. f. Bakteriol., 1911, lx, 223.

[7] Jahrb. f. Kinderheilk., 1912, lxxxvi, 507; Der Skorbut der kleinen Kinder., Stuttgart, 1913.

[8] Boston Med. and Surg. Jour., 1913, clxix, 232.

[9] Fortschr. a. d. Geb. d. Rontgenstrählen, 1903–1904, vii, 231 and 291; 1906–1907, x, 1; 1908, xviii, supplement.

[10] Jahrb. f. Kinderheilk., 1912, lxxv, 663.

[11] Arch. f. exper. Path. u. Pharmakol., 1913, lxxxiii, 313.

Schmorl's work was confirmed by M. Masslow,[12] who described the microscopic changes in the bones in almost identical language, and noted the absence of hemorrhages; he also demonstrated a marked phosphorus deficiency in the bones and all the viscera in his laboratory animals. Masslow concludes, "That in the pathogenesis of disturbances of the osseous system phosphorus plays a distinct role."

Bahrt and Edelstein[13] found postmortem a decrease of ash in the bones especially of calcium and phosphorus very much as in rickets; there was also an increase of the water content of the bones and a diminished calcium content of the muscles.

Morgen and Beger[14] found that rabbits fed on oats alone lost weight and appetite. While an addition to the oats of dicalcium phosphate or sodium chloride had no effect, calcium carbonate caused an arrest of the loss of weight, and the animals did not loose their appetite, but nevertheless they finally died, often with evidence of paralysis. At autopsy there was no pathological change found in the bones or in the alimentary canal, but a marked emaciation and an anemia. The addition of sodium bicarbonate to the diet prevented the loss of weight or caused an immediate rise in the weight of the animal previously fed on oats alone; further, they remained in good health and appetite. The authors believe, therefore, that the cause of the deleterious action of the restricted oats diet is not calcium deficiency but an acid poisoning, as the basic mineral matter of the oats is not sufficient to neutralize the acids which arise during the oxidation of the proteins, namely, phosphoric and sulphuric acids.

Scherer[15] observed in southwest Africa that scurvy prevails when there is a deficiency in the calcium content and an increased alkalinity of the drinking water. He believes that a balance normally exists between the alkalies, potassium and sodium, and the alkaline earths, calcium and magnesium, and that this is disturbed when scurvy appears.

Alex Ingier[16] reproduced scurvy both in the fetus and in the mother guinea-pig by a diet restricted to oats and water. The scorbutic changes in the skeleton were greatest in the earlier embryonic stage. The mother showed signs of the disease at an early period and was more severely affected than a non-pregnant animal. The pathological picture produced resembled that seen in Barlow's disease, by the diminished or even absent bone formation, by the existence of hemorrhages in the bone marrow; by the formation of the structural marrow (gerüst-mark), and by the occurrence of

[12] Biochem. Ztschr., 1914, lxiv, 106.
[13] Ztschr. f. Kinderheilk., 1913, ix, 415.
[14] Ztschr. f. physiol. Chemie, 1915, xciv, 324.
[15] München. med. Wchnschr., 1914, lxi, 1282.
[16] Jour. Exper. Med., 1915, xxi, 525.

fractures. Ingier admits that no experiment has so far succeeded in a direct demonstration of the possible lacking substance in the scorbutic diet.

A. F. Hess and M. Fish[17] found a slightly diminished clotting power of the blood plasma in infantile scurvy, but this defect was not due to a calcium insufficiency. They reported several cases of scurvy which developed in infants fed on milk which was pasteurized by heating to 145° F. for thirty minutes; they were cured by raw milk or fruit juices. Orange juice was found not to loose its efficiency by boiling for ten minutes. The juice of the orange-peel was found as efficacious as that of the fruit itself. They also found that potato was an excellent antiscorbutic and may be added to pasteurized milk instead of barley-water. In a later paper A. F. Hess[18] pointed out that several important symptoms of scurvy have not received the attention they merit. Thus, enlargement of the heart and especially of the right ventricle could be demonstrated by percussion and the roentgenogram. Edema is also a constant symptom in the upper eyelids and over the long bones. Lastly, the nerves may be involved, as shown by increased knee-kicks, superficial tenderness of the limbs, and neuroedema of the optic disks.

Scurvy has been produced in the monkey by Hart and Talbott, but will be referred to at length in a subsequent paper.

A review of the literature of this subject would not be complete without a brief mention of some recent work on beriberi, which is also one of the so-called "deficiency diseases."

In 1912 Susuki, Shimamura, and Odake[19] succeeded in isolating from rice-bran a crystalline picrate from which nicotinic acid and a carbohydrate were obtained. These two bodies are probably inactive; the active substance they had, so far, not isolated, but for it they suggested the name "oryzanin."

Casimir Funk[20 21 22 23] classifies under the term "deficiency diseases" beriberi, polyneuritis in birds, epidemic dropsy, scurvy, experimental scurvy in animals, infantile scurvy, ship-beriberi, and pellagra. He showed that the various curative extracts are essentially phosphorus-free, and therefore the phosphorus theory of Schaumann is still further shattered. He found that the curative substance was present in small amounts in rice (about 0.1 gram per kilogram). He believed it to be an organic base, to which he has given the name "vitamine." This, like uracil and thymine, belongs to the pyrimidine group, and is probably a constituent of nucleic acid.

[17] Amer. Jour. Dis. Child., 1914, viii, 385.
[18] Jour. Am. Med. Assn. 1915, lxv, 1003.
[19] Biochem. Ztschr., 1912, xliii, 89.
[20] Jour. Physiol., 1911, xliii, 395; 1912, xliv, 50; 1912, xlv, 75.
[21] Jour. State Med., 1912, xx, 341.
[22] München. med. Wchnschr., 1913, lx, 2614.
[23] Die Vitamine, Wiesbaden, 1914.

Animals whose food shows a deficiency in this substance loose weight to an enormous extent and cannot be maintained in nitrogen-equilibrium, not even with nitrogen and caloric-rich food. He further believes that scurvy, Barlow's disease, and probably also pellagra and rickets, arise from an absence from the food of this vitamine, and suggests for the group the name "avitaminoses."

Schaumann[24] later confirmed Funk's work on the phosphorus-free nature of the crystalline substance isolated from rice-bran. He, however, believes that this body plays but an intermediate role in the cure of the disease, and that since relatively small amounts are sufficient to cure, and since the effect is also quite persistent, he believes that this activator is of the nature of an enzyme.

Much has been written about the deficiency diseases in the past twelve months, and all are agreed about the close affinity of rickets, infantile scurvy, scurvy, experimental scurvy of the guinea-pig, ship-beriberi, beriberi, polyneuritis gallinarum, and possibly pellagra. Thus, Darling[25] and Brown[26] have both emphasized the close similarity between scurvy and beriberi, clinically, etiologically, and pathologically. Brown writes: "The relation between scurvy, rickets, tetany, and beriberi is intimate and apparently depends upon the balance of the various salts of the body, particularly sodium and potassium on the one hand, and calcium and magnesium on the other, while the position of phosphorus is more variable, although the majority of observers place it along with calcium and magnesium." Excessive retention of sodium and potassium over calcium and magnesium may produce tetany and always rickets.

II. Experimental Scurvy of the Guinea-pig. We first decided to confirm for ourselves the production of experimental scurvy in the guinea-pig. Full-grown healthy young animals were taken and after becoming accustomed to their confinement in a metabolism cage they were found to be in good health and holding their weight. They were then placed on a diet consisting of oats and water. Two series, the first consisting of six and the second of two guinea-pigs, were studied. These animals all gradually lost their appetite, became listless, and walked with difficulty, emaciated considerably, and just before death (which occurred in from twenty-eight to thirty days) developed bloody diarrhea and sometimes hematuria. They were promptly autopsied, and gross and microscopic changes of scurvy found in all the animals. Illustrative protocols follow:

*Experiment I.* Guinea-pig No. 5, weighed at beginning of experiment (June 28) 616 grams and at day of death (July 27) 266 grams, a loss of 350 grams, or 57 per cent. of body weight. Macroscopi-

[24] Arch. f. Schiff. u. trop. Hyg., 1913, xvi, 350.
[25] Jour. Am. Med. Assn., 1914, lxiii, 1290.
[26] Arch. Pediat., 1915, xxxii, 74.

cally, there was slight looseness of the teeth, but no sponginess of the gums and no intramuscular or serous hemorrhages were found. Microscopic changes were noted as follows: In the femur a section was cut through the head transversely. The blood spaces are seen to be discreet and uncrowded. There is no subperiosteal hemorrhage. The bony trabeculæ stain lightly with hematoxylin. The section through the head shows no change from normal controls. A longitudinal section was cut through the condyles of the femur. There is slight subperiosteal hemorrhage all along the portion proximal to the epiphyseal line. This line is distinguished by the evidence of increased calcium deposit along its proximal border, as shown by the intensity with which the trabeculæ here take the alum-hematoxylin stain. This reaction is most dense in immediate relation to the line, but is continued along the shaft for 1 or 2 mm. The epiphyseal line also marks a distinct difference in blood distribution. On the distal side the blood spaces are discreet and uncrowded. On the proximal side of the epiphyseal line, and extending up the shaft for 2 or 3 mms. the blood spaces are overcrowded and frequently confluent, allowing pools of blood to form. No distinction in the types of cells seen on the two sides of the line could be determined. A section through the head of the tibia showed the identical changes above described. A section through the costochondral junction was studied. Here a slight subperiosteal hemorrhage was noted, and in the bony tissue an overcrowding of the blood spaces with apparent breaking down of the bony partitions separating the same. No unusual degree of calcification was noted. The kidneys were found not to be congested. The epithelium and the glomeruli are intact and there is no interstitial deposit. The spleen shows no congestion, no increase in size or interstitial change, and no increase of red-cell content. The liver is not congested and there is no degeneration of the parenchyma or fatty change in any part. The heart muscle shows its striation well, and there are no granulations or vacuolization of the nuclei. There are no fatty changes in the muscle fibers and no interstitial deposit.

*Summary of Microscopic Examination.* Viscera nagative. Subperiosteal hemorrhages in the vicinity of the epiphyses of the long bones and at the costochondral junctions. Hemorrhages into the bone substance proximal to the epiphyseal line of the long bones and in the bony part of the ribs adjacent to the cartilage of the same. A reaction in the trabeculæ of the long bones just proximal to the epiphyseal line and most marked in immediate proximity to the line, indicating that the trabeculæ here have a deposit of lime-salts markedly in excess of that on the distal side of the epiphysis or in the shaft of the bone.

*Experiment II.* September 15, two guinea-pigs from the same litter, three months old, were placed in a metabolism cage and given oats and water *ad libitum*. The urine and feces were not collected.

*Guinea-pig No.* 1. Large, white male; weight (September 15) 836.51 grams; September 26, 768.00 grams. October 6, it was noticed that the pig was eating little if any; it was very quiet and its fur appeared ruffled. October 9, it weighed 623 grams, a loss of 25 per cent. of body weight. October 11, (the twenty-seventh day) it was so weak that it was chloroformed, and a roentgen-ray picture revealed at the lower epiphyseal line of the left humerus a wide, dense, white line. The autopsy, two hours postmortem, showed slight looseness of the teeth but no swelling of the gums or hemorrhage into the mucous membrane of the mouth or around the hairs of the snout. In the muscles of the biceps and the pectoralis major of the left foreleg a large hemorrhage, 1 cm. in diameter, was found; but none elsewhere; the peritoneal cavity appeared normal. The intestines were strikingly pale as compared with those of guinea-pig No. 2; the liver and spleen appeared normal; the bladder was dilated with urine and revealed a few hemorrhages into the mucosa. On opening the stomach a few petechial hemorrhages were also found in the mucosa. On opening the thorax the lungs were found to be markedly enlarged, particularly in the dependent portions. The four extremities were carefully dissected, particular attention being paid to the condition of the muscles around the joint cavities; no hemorrhages or evidences of disease could be found, except perhaps a little fragility of the bones, but this was hard to estimate. Specimens were removed from all the organs and preserved in 10 per cent. formalin.

*Guinea-pig No.* 2. A large brown male, weighing 811.02 grams September 15; placed on the same oats and water diet; September 26, it weighed 734.7 grams and October 9, 578.5 grams, a loss of 22 per cent. of body weight. It too began to fail and lose appetite October 6. A roentgen-ray plate was taken October 11, which also revealed a little increase in density of the shadow at the lower epiphyseal line of the left humerus. It died under the anesthetic and an autopsy was performed two hours later. It then weighed 541 grams. Autopsy: Gums appeared relatively bluish, though no visible swelling, no ecchymosis except between the two lower teeth, where the gums appeared a trifle hemorrhagic. The teeth were lusterless, and were easily moved with a light pair of forceps, though not loose enough to be readily extracted; there was a hemorrhage into the muscles on the thoracic surface of the left side. This was about the size of a pea. In the same region on the right a small hemorrhage was seen. No other intramuscular hemorrhage could be found. Upon opening the abdomen the small intestines appeared deeply congested, and there were fair quantities of blood which oozed from the lumen when incised. On the anterior surface of the left lobe of the liver was a large, irregular, yellowish-white area, the size of a nickel, which was removed for examination. The bladder was distended with urine and contained numerous areas of ecchy-

mosis similar to those in guinea-pig No. 1, but more extensive. The thoracic cavity was free from blood, but the lungs appeared large and distinctly hemorrhagic. Sections were made from all the organs. The four extremities were carefully dissected, particular attention being paid to the periarticular tissues; no evidence of hemorrhage could be found. The joint cavities appeared normal. One of the long bones broke with very slight traumatism. All specimens were preserved in 10 per cent. formalin solution.

Microscopic changes were noted as follows: In guinea-pig No. 1 the humerus shows no subperiosteal hemorrhage. The red corpuscles seem more numerous and more generally distributed on the distal side of the epiphyseal line. The line is dense and the deposit of lime-salts is slightly in excess on the diaphyseal side.

The ulna shows no subperiosteal hemorrhage and no changes in the blood distribution. There is at no point any excess of calcification.

The femur was cut through its condyle. There is no subperiosteal hemorrhage. The blood seems in excess on the distal side of the epiphyseal line. The line itself is dense and the trabeculæ of the diaphysis are more infiltrated with lime-salts than those of the epiphysis.

The tibia shows a very slight subperiosteal hemorrhage. The distribution of blood is uneven, though none of the spaces are crowded. The epiphyseal line is dense and the calcification of the trabeculæ of the diaphysis is more marked than that of the epiphysis.

In none of the bones examined was any change in the cellular elements of the marrow noticed.

The lung is slightly congested, but there is no infiltration.

The heart muscle has lost its striation, but the nuclei are not swollen or vesiculated.

The kidney shows a marked degree of postmortem autolysis.

In Guinea-pig No. 2, the sections through the head of the humerus show well-marked subperiosteal hemorrhage. The marrow spaces seem more numerous in the diaphysis and the erythrocytes appear more numerous than normal. The epiphyseal line is well marked and the trabeculæ of the diaphysis are more deeply stained with hematoxylin than those of the epiphysis. The cellular constituents of the marrow are red blood cells and myelocytes, which are granular and stain some with basic and some with acid dyes. There are also quite a number of multinucleated cells. All these elements are evenly disturbed on both sides of the epiphyseal line.

A section through the lower end of the humerus shows a subperiosteal hemorrhage. The epiphyseal line does not appear in the section.

A longitudinal section through the condyles of the femur shows no subperiosteal hemorrhage. There is a very slight diaphysis.

There is no apparent difference in the marrow spaces on either side of the line. The cellular constituents are as above described and evenly distributed.

A section through the shaft of the femur in a longitudinal direction shows no subperiosteal hemorrhage and no excessive calcification. The head of the tibia shows no subperiosteal hemorrhage, but the blood spaces of the diaphysis seem crowded and in some places coalesced. There is a well-marked epiphyseal line showing increased calcium salts, which are also apparent in the trabeculæ of the diaphysis. The cellular constituents are of the same character and distribution as was described in connection with the humerus.

The kidney shows a moderate degree of congestion and the cells are in a state of degeneration in the granular stage. The lungs are congested but not infiltrated.

Unfortunately, in view of a recent publication by Hess,[27] sufficient attention was not paid to the condition of the heart. Hess found in infantile scurvy a tendency to dilatation of the heart, and more especially of the right ventricle.

From these two experiments we felt satisfied that we could reproduce scurvy in the guinea-pig and that the pathological changes noted by Holst and Frölich occurred in our animals.

III. Mineral Metabolism of Normal Guinea-pig. The next point was to determine the normal metabolism of the guinea-pig, as we could find almost nothing in the literature on this subject, and letters of inquiry to various chemists in agricultural colleges, such as H. Grindley, of Illinois, and E. V. McCollum, of Wisconsin, were answered in the negative.

Lukjanow[28] gives the respiratory metabolism but nothing further.

Alezias[29] described the physical characters of the urine and gave the daily average output per 100 grams of body weight, of urea (0.10 grams), of the phosphates (0.003 gram), and of chlorine (0.07 gram). Hunter[30] found that the total nitrogen varied between 1.1 to 3.3 grams pro diem in the normal guinea-pig.

A metabolism cage made by the August Maag Company, of Baltimore, was used. In it was placed a healthy young guinea-pig of 692 grams. The urine was collected in a bottle containing dilute acetic acid and toluol. At the end of twenty-four hours the urine was placed in a glass-stoppered bottle in the ice-box. The feces were carefully picked out of the cage and placed in a wide-mouthed, glass-stoppered bottle until the end of the period, when they were dried to constant weight *in vacuo*, ground to fine powder and put away in a sealed bottle until analyzed. The cages were washed down with distilled water and the washings added to the urine after

[27] Loc. cit.
[28] Ztschr. f. physiol. Chem., 1884, viii, 313.
[29] Compt. rend. Soc. de biol., 1896, xlviii, 213; 1897, xlix, 413.
[30] Jour. Biol. Chem., 1914, xviii, 387.

the latter had been measured. The food, which consisted of oats, white turnips, or white cabbage, was carefully weighed. In Experiment III the food was not analyzed directly but the various mineral constituents were estimated from Koenig's valuable tables. Unfortunately, in the first two periods the guinea-pig lost weight, but was not apparently ill; in the last three periods it gained in weight slightly. Five periods of from five to nine days each were studied in the first experiment and gave the following figures, the first, as far as we know, on the nitrogen and mineral metabolism of this animal. (See Table I.) These figures differ a little from the normal period of Experiments VIII and IX, but a different diet was used.

TABLE I.—NORMAL OUTPUT PER GUINEA-PIG PER DAY. EXPERIMENT 2.

| | Nitrogen. | | Sulphur. | | Chlorine. | | Phosphorus. | | Sodium. | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Urine. | Feces. | Urine. | Feces. | Urine. | Feces. | Urine. | Feces. | Urine. | Feces. |
| Maximum | 0.1761 | 0.0368 | 0.0394 | 0.0082 | Only one period | | 0.0099 | 0.0060 | 0.0147 | 0.0082 |
| Minimum | 0.1628 | 0.0228 | 0.0220 | 0.0064 | | | 0.0076 | 0.0042 | 0.0116 | 0.0035 |
| Average | 0.1712 | 0.0239 | 0.0329 | 0.0072 | 0.0092 | 0.0010 | 0.0087 | 0.0051 | 0.0131 | 0.0058 |

| | Potassium. | | Calcium. | | Magnesium. | | Diet. |
|---|---|---|---|---|---|---|---|
| | Urine. | Feces. | Urine. | Feces. | Urine. | Feces. | |
| Maximum | 0.1260 | 0.0136 | 0.0091 | Only one period | 0.0056 | Only one period | Oats and white turnips or white cabbage. |
| Minimum | 0.0962 | 0.0064 | 0.0049 | | 0.0048 | | |
| Average | 0.1111 | 0.0100 | 0.0070 | 0.0021 | 0.0052 | 0.0013 | |

IV. MINERAL METABOLISM OF SCURVY IN THE GUINEA-PIG. Having developed our technic and overcome many small difficulties too numerous to mention, we started two more series, two young guinea-pigs in each series, and ran them for longer periods (fourteen days) on a normal weighed and analyzed diet of carrots, oats, and water until such time as they had been gaining in weight and were accustomed to the laboratory environment. They were then placed on the restricted oats diet and the urine and feces collected in fourteen-day periods. All four animals developed typical symptoms and died but in a rather shorter period than in our former series, namely, in from eighteen to twenty-two days.

*Experiment VIII.* December 1, 1913, at midday, two young male guinea-pigs from the same litter were placed in a metabolism cage and given a carefully weighed diet of fresh carrots, oats, and water. At the beginning of the period their combined weight was 985 grams. At the end of fourteen days their combined weight was 984.8 grams, showing that they were holding their own. At the end of this normal period, namely, December 15, 1913, the carrots were withdrawn and they received only oats and water. December 17, the urine and feces were discarded and the second or scurvy period started. By the end of the period, after sixteen days of the restricted feeding, both animals were evidently ill, with ruffled coat, loss of appetite, and bodily inactivity; one passed soft and tarry

feces. They now weighed 664.9 grams, having lost 319.9 grams in sixteen days. Period III was now started on December 31, but at 5 P.M., January 2, 1914, or after nineteen days on the restricted diet, one guinea-pig died (No. 1). January 3, 1914, the urine of the second animal was noted to be bloody, and it died January 5, or after twenty-two days on the restricted diet.

Postmortem their combined weight was 544.3 grams, or a loss of 45 per cent. body weight. In both animals the gums were swollen and bluish, but revealed no hemorrhages. The teeth were loose and readily extracted. There were no hemorrhages found in the muscles or into the various serous cavities. The condition of the heart was not noted. The large intestine contained dark fluid material, probably altered blood.

*Histology.*[31] Sections were made from the upper and lower end of the humerus and the condyles of the femora and the head of the tibiæ. Careful study of these showed slight but definite changes, as in Experiment I, namely, subperiosteal hemorrhages, with extravasation of blood into the intertrabecular spaces of the epiphysis and alterations in the bone marrow. There was some thickening of the epiphyseal line but no evidence of increased deposit of lime-salts. The heart muscle presented poor striation but no nuclear changes.

*Experiment IX.* December 1, 1913, two young males from the same litter were placed in a metabolism cage and given a carefully weighed diet of fresh carrots, oats, and water. At the beginning of the normal period their combined weight was 990.5 grams; at the end of fourteen days it was 1077.7 grams; in other words, these animals gained 87.2 grams under similar conditions as those of Experiment VIII. They ate voraciously and were possibly younger animals which had not reached their full growth at the beginning of the experiment.

December 15, the carrots were withdrawn from the dietary. December 17, the second period was begun. December 31, the end of the second period (*i. e.*, after sixteen days on the restricted diet) both animals showed a ruffled coat, loss of appetite, and bodily inactivity, while both were passing dark, loose stools. They now weighed 733.3 pounds, having lost 344.4 grams. Period III was now started January 2, 1914. One guinea-pig died eighteen days after the onset of the oats diet. January 3, the other animal passed bloody urine, and on January 5 it died after twenty-one days on the restricted diet.

Postmortem their combined weight was 610.8 grams, or a loss of 56.6 per cent. of body weight. They showed the same blue color to the gums and the teeth were loose. There were no hemorrhages into the gums, muscles, joints, or serous surfaces found. The

[31] For the histological study of our animals we wish to express our thanks to Dr. Royce, the pathologist of the University Hospital.

large intestine was filled with dark, tarry material, probably in great part altered blood.

*Histology.* Sections were made from the head of the humerus, the head, and the lower end of the radius, the condyles of the femur and the head of the tibia. While subperiosteal hemorrhage was not so frequent, there were constant hemorrhages into the trabeculæ spaces of both epiphyses and diaphyses, with fibrin in considerable amounts distributed in masses in some areas and as a network in others. The epiphyseal line too was usually thickened and stained deeply with hematoxylin. In one animal the lung showed infiltration of the walls of the alveoli with leukocytes, while some of the alveoli were filled with fibrin, red, and white blood cells. The heart was not examined.

From the above protocols it will be seen that we had succeeded in reproducing both gross and microscopic changes in our animals which have been considered as pathognomic of scurvy in the guinea-pig.

*Procedure.* Profiting by our experience in former experiments the urine was collected under toluol in a flask to which 5 c.c. of dilute acetic acid were added to render the urine acid and to prevent decomposition. It was daily collected and stored in a glass-stoppered vessel and placed in an ice-box. At the end of each period the wire floor, bottom, and sides of the cage were carefully washed down with distilled water and the washwater added to the urine and further diluted to 1500 c.c. Varying amounts of this were taken for analysis and duplicate estimations were made and repeated until they corresponded within the experimental error.

Every two days the feces were carefully picked out with clean forceps and in this way separated from the hulls and oats in the bottom of the cage. They were placed in wide-mouthed glass-stoppered bottles and preserved in the ice-box until the end of the period. They were then dried to constant weight *in vacuo* as described in a former paper, ground in a mill to a fine powder, placed in a glass-stoppered bottle, sealed with paraffin, and examined for the various constituents at our leisure. The nitrogen content of the distillate was, of course, added.

The intake of the various elements was calculated as follows: A large supply of oats and carrots was obtained at the outset of the experiment. The water content of each was determined and the material placed in sealed containers. Weighed portions were placed at the disposal of the animals. The unconsumed food, including the oat-hulls, was then dried to constant weight, powdered and analyzed, and the mineral content in each instance deducted from that found in the oats and carrots which had been placed in the cage.

The first period of fourteen days represents the normal period on a weighed mixed diet for two healthy animals. (See Tables II and III.)

TABLE II.

| Period | No. days. | Weight in grams. | Diet. | Urine in c.c. +washwater | Dried feces. | Total nitrogen. | | | | Total sulphur. | | | | Chlorin. | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Intake. | Output. | | Balance. | Intake. | Output. | | Balance. | Intake. | Output. | | Balance. |
| | | | | | | | Urine. | Feces. | | | Urine. | Feces. | | | Urine. | Feces. | |
| Experiment 8 | | | | | | | | | | | | | | | | | |
| 2 guinea-pigs | | | | | | | | | | | | | | | | | |
| I | 14 | At onset =985.0 At end =984.8 loss=0.2 | Carrots =94.45 Oats=461.7 Hulls left =20.3 | 1500 c.c. | 73.94 | Carrots =1.4575 Oats =10.7920 | 3.6435 | 2.5637 | 6.0423+ | Carrots =0.1322 Oats =0.7504 | 0.4740 | 0.2309 | 0.1786+ | Carrots =0.1916 Oats =0.4730 | 0.2612 | trace[3] | 0.4034+ |
| II | 14 | At onset =984.8 At end =664.9 Loss=319.9 | Carrots =0 Oats=209.0 Hulls left =15.77 | 1500 c.c. | 46.72 | Carrots =0 Oats =4.7769 | 5.9850 | 1.5582 | 2.7663− | Oats =0.3286 | 0.4019 | 0.1784 | 0.2517− | Carrots =0 Oats =0.2027 | 0.2471 | trace[3] | 0.0444− |
| Experiment 9 | | | | | | | | | | | | | | | | | |
| 2 guinea-pigs | | | | | | | | | | | | | | | | | |
| I | 14 | At onset =990.5 At end =1077.7 Gain =87.2 | Carrots =176.8 Oats =478.02 Hulls left =27.97 | 3000 c.c. | 81.5 | Carrots =2.7320 Oats =11.0640 | 3.7905 | 3.1104 | 6.8951+ | Carrots =0.2475 Oats =0.7652 | 0.5822 | 0.2659 | 0.1646+ | Carrots =0.3586 Oats =0.4778 | 0.4082 | trace[3] | 0.4282+ |
| II | 14 | At onset =1077.7 At end =733.3 Loss=344.4 | Carrots =0 Oats=270.5 Hulls left =33.3 | 1500 c.c. | 59.27 | Carrots =0 Oats =5.9619 | 5.5755 | 2.4854 | 2.0930− | Oats =0.4033 | 0.3607 | 0.1392 | 0.1166− | Carrots =0 Oats =0.2401 | 0.1707 | trace[3] | 0.0694+ |

| Period. | Total phosphorus. | | | | Sodium. | | | | Potassium. | | | | Calcium. | | | | Magnesium. | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intake. | Output. | | Balance. | Intake. | Output. | | Balance. | Intake. | Output. | | Balance. | Intake. | Output. | | Balance. | Intake. | Output. | | Balance. |
| | | Urine. | Feces. | | | Urine. | Feces. | | | Urine. | Feces. | | | Urine. | Feces. | | | Urine. | Feces. | |
| Experiment 8 | | | | | | | | | | | | | | | | | | | | |
| 2 guinea-pigs | | | | | | | | | | | | | | | | | | | | |
| I | Carrots =0.3228 Oats =1.8950 | .6158 | .9065 | .6961+ | Carrots =0.9161 Oats =1.4224 | 1.4163 | 0.2884 | 0.5747+ | Carrots =1.8420 Oats =2.3590 | 1.5468 | 0.5693 | 2.0849+ | Carrots =0.3729 Oats =0.3108 | .1170 | .1701 | .3966+ | Carrots =0.1392 Oats =0.3982 | .0795 | .2218 | .2361+ |
| II | Carrots =0 Oats =0.8334 | .5339 | .5251 | .2256− | Carrots =0 Oats =0.5805 | 0.4792 | 0.2056 | 0.1043− | Carrots =0 Oats =0.0239 | 1.3406 | 0.3831 | 0.6998− | Carrots =0 Oats =0.1291 | .1704 | .1542 | .1955− | Carrots =0 Oats =0.1747 | .6708 | .0841 | .0198+ |
| Experiment 9 | | | | | | | | | | | | | | | | | | | | |
| 2 guinea-pigs | | | | | | | | | | | | | | | | | | | | |
| I | Carrots =0.6043 Oats =1.9368 | .5983 | .9991 | .9437+ | Carrots =1.7150 Oats =1.3734 | 1.1048 | 0.3260 | 1.6576+ | Carrots =3.4470 Oats =2.3964 | 3.8387 | 0.6439 | 1.3608+ | Carrots =0.6630 Oats =0.3095 | .2358 | .1793 | .5574+ | Carrots =0.2475 Oats =0.4063 | .1441 | .2201 | .2896+ |
| II | Carrots =0 Oats =1.0302 | .6149 | .7273 | .3120− | Carrots =0 Oats =0.6791 | 0.3562 | 0.2845 | 0.0384+ | Carrots =0 Oats =1.2403 | 0.9469 | 0.4860 | 0.1926− | Carrots =0 Oats =0.1446 | .1080 | .1837 | .1471− | Carrots =0 Oats =0.2151 | .0698 | .0948 | .0505+ |

[3] Not weighable.

TABLE III.

OUTPUT PER GUINEA-PIG PER DAY.

| | Nitrogen. | | Sulphur. | | Chlorine. | | Phosphorus. | |
|---|---|---|---|---|---|---|---|---|
| | Urine. | Feces. | Urine. | Feces. | Urine. | Feces. | Urine. | Feces. |
| Normal period VIII[1] | 0.1301 | 0.0916 | 0.0170 | 0.0082 | 0.0093 | trace | 0.0220 | 0.0324 |
| Normal period IX[1] | 0.1353 | 0.1110 | 0.0208 | 0.0095 | 0.0146 | trace | 0.0214 | 0.0357 |
| Average | 0.1327 | 0.1013 | 0.0189 | 0.0088 | 0.0119 | trace | 0.0217 | 0.0341 |
| Abnormal period VIII[2] | 0.2140 | 0.0557 | 0.0143 | 0.0064 | 0.0088 | trace | 0.0190 | 0.0190 |
| Abnormal period IX[2] | 0.1991 | 0.0888 | 0.0129 | 0.0057 | 0.0061 | trace | 0.0229 | 0.0260 |
| Average | 0.2065 | 0.0723 | 0.0136 | 0.0061 | 0.0075 | trace | 0.0210 | 0.0230 |

| | Sodium. | | Potassium. | | Calcium. | | Magnesium. | |
|---|---|---|---|---|---|---|---|---|
| | Urine. | Feces. | Urine. | Feces. | Urine. | Feces. | Urine. | Feces. |
| Normal period VIII[1] | 0.0506 | 0.0103 | 0.0552 | 0.0203 | 0.0042 | 0.0061 | 0.0028 | 0.0079 |
| Normal period IX[1] | 0.0394 | 0.0116 | 0.1371 | 0.0230 | 0.0084 | 0.0064 | 0.0051 | 0.0078 |
| Average | 0.0450 | 0.0110 | 0.0962 | 0.0217 | 0.0063 | 0.0063 | 0.0039 | 0.0079 |
| Abnormal period VIII[2] | 0.0171 | 0.0073 | 0.0466 | 0.0137 | 0.0061 | 0.0055 | 0.0025 | 0.0030 |
| Abnormal period IX[2] | 0.0127 | 0.0101 | 0.0338 | 0.0174 | 0.0038 | 0.0065 | 0.0025 | 0.0034 |
| Average | 0.0149 | 0.0087 | 0.0402 | 0.0156 | 0.0050 | 0.0060 | 0.0025 | 0.0032 |

INTAKE PER GUINEA-PIG PER DAY.

| | Nitrogen. | Sulphur. | Chlorine. | Phosphorus. | Sodium | Potassium. | Calcium. | Magnesium. |
|---|---|---|---|---|---|---|---|---|
| Normal period VIII[1] | 0.4374 | 0.0315 | 0.0237 | 0.0792 | 0.0814 | 0.1500 | 0.0244 | 0.0192 |
| Normal period IX[1] | 0.4927 | 0.0361 | 0.0299 | 0.0907 | 0.1103 | 0.2087 | 0.0347 | 0.0233 |
| Average | 0.4650 | 0.0338 | 0.0268 | 0.0850 | 0.0959 | 0.1794 | 0.0296 | 0.0213 |
| Abnormal period VIII[2] | 0.1706 | 0.0177 | 0.0072 | 0.0298 | 0.0207 | 0.0365 | 0.0046 | 0.0062 |
| Abnormal period IX[2] | 0.2129 | 0.0144 | 0.0086 | 0.0368 | 0.0242 | 0.0443 | 0.0051 | 0.0077 |
| Average | 0.1918 | 0.0131 | 0.0079 | 0.0333 | 0.0225 | 0.0404 | 0.0049 | 0.0070 |

AVERAGE BALANCE PER GUINEA-PIG PER DAY.

| | Nitrogen. | Sulphur. | Chlorine. | Phosphorus. | Sodium. | Potassium. | Calcium. | Magnesium. |
|---|---|---|---|---|---|---|---|---|
| Average intake, normal periods | 0.4650 | 0.0338 | 0.0268 | 0.0850 | 0.0959 | 0.1794 | 0.0296 | 0.0213 |
| Average output, normal periods | 0.2340 | 0.0277 | 0.0119 | 0.0558 | 0.0560 | 0.1179 | 0.0126 | 0.0118 |
| Balance, normal periods | +0.2310 | +0.0061 | +0.0149 | +0.0292 | +0.0399 | +0.0615 | +0.0170 | +0.0095 |
| Average intake, abnormal periods | 0.1918 | 0.0131 | 0.0079 | 0.0333 | 0.0225 | 0.0404 | 0.0049 | 0.0070 |
| Average output, abnormal periods | 0.2788 | 0.0197 | 0.0075 | 0.0440 | 0.0236 | 0.0558 | 0.0110 | 0.0057 |
| Balance, abnormal periods | −0.0870 | −0.0066 | +0.0004 | −0.0107 | −0.0011 | −0.0154 | −0.0061 | +0.0013 |

The second period of fourteen days represents the abnormal or scurvy period. It was preceded by a fore-period of two days, the urine and feces of which were discarded.

The third period was unfortunately so short and the animals were eating so little and excreting so little urine and feces that enough material was not obtained for purposes of analysis of all the constituents. These were kept, however, in case there was a striking increase or decrease in the balance of any one mineral, which could be confirmed in this period.

*Analytical Method.* The methods were similar to those used in Experiment I. Extra precautions were necessary to render the silica present in some of the material insoluble. This was usually accomplished by evaporating the acid ash-extract to dryness on

the water bath, then drying at 110 to 120° for two hours in the drying oven. This precaution was necessary in the estimation of the calcium in the food, urine, and feces.

V. Discussion of Results. The animals employed in these experiments were vigorous but immature. They retained considerable nitrogen and two gained in weight during the normal period. When the diet was restricted to oats an insufficient amount of nitrogen and an inadequate number of calories were consumed, with a consequent loss of nitrogen and body weight. This factor must be borne in mind in the interpretation of the analytical results. It is impossible with the available data to estimate the role which starvation played in these experiments. However, it is well to note that starvation alone will not produce the pathological changes observed, as shown by Holst and Frölich.

*Nitrogen, Sulphur, and Phosphorus.* The excretion of these elements during the abnormal periods was remarkably high, and this is hardly to be explained by starvation alone. For example, during the first normal period the animals consumed about 12 grams of nitrogen and excreted 3.64 grams in the urine, and 2.56 grams appeared in the feces. In the abnormal period they ingested 4.77 grams, but excreted about 6 grams in the urine and 1.56 grams in the feces. This may indicate increased protein katabolism.

*Sodium and Chlorine.* During the first abnormal period there was but a slight loss, and during the second a gain in sodium and chlorine. One might assume that sodium chloride did not play an important role in the etiology of this disease, although the bulk of the sodium is evidently not excreted in this form.

*Potassium.* This element is more abundant in the vegetable diet administered than any of the other bases. Considerable quantities were retained during the normal periods. The loss of this element during the abnormal periods is greater than that of sodium.

*Calcium and Magnesium.* A considerable part of the calcium is excreted through the urine. The amount excreted during the abnormal periods is notably high. Magnesium is the only element which was consistently retained during the four periods. The loss of calcium during the "oats" period may partly account for the diminished bone formation observed in this disease.

VI. Conclusions. An examination of the evidence, both experimental and clinical, leads to the view that scurvy, and perhaps the allied diseases as well, are due to the absence of certain substances in the dietary. The lack of this material appears to have a profound effect on the mineral metabolism of the guinea-pig.

# THE PRINCIPLES AND PRACTICE OF REGISTERING HEART SOUNDS BY DIRECT METHODS.[1]

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Introduction. A simple method of registering heart sounds in conjunction with other graphic tracings, or the electrocardiogram, is frequently desirable. No means of accomplishing this has proved entirely satisfactory. The most successful procedure hitherto devised for recording sounds is that of Einthoven[2] and his associates.[3] The sound vibrations are transformed by the aid of a microphone and secondary coil into electrical variations which are recorded by the string galvanometer. In order to use this procedure in connection with the electrocardiograph two galvanometers are required, a luxury not enjoyed by most institutions. The direct registration of heart sounds, meaning thereby the transmission of sound vibrations to membranes capable of directly recording these oscillations photographically, seems to be the most expeditious procedure.

The impression may easily be gained, in reading the literary champions of various methods, that this may readily be accomplished by installing their particular form of apparatus. An actual inspection of the published records is sufficient to convince even the uninitiated that the total number of true sound-records obtained in this way is not very great. The sound-records obtained by the phonocardiographic method of Einthoven have set a standard by which the records obtained by direct registration may well be judged. They show (Fig. 1 *A*) that the vibrations start from a horizontal line and oscillate above and below it, that the frequency as well as the amplitude alters from one vibration to another, and that these characteristics vary in different individuals. Most of the published records taken with direct methods show no similarity to these tracings. This is the case of the records published by Bull,[4] Van Zwaluenberg and Agnew,[5] Weiss and Joachim,[6] Gerhartz,[7] and Ohm,[8] photographic reproductions of some of which are shown in Fig.

[1] Received for publication October 7, 1916.
[2] Arch. f. d. gesam. Physiol., 1907, cxvii, 461; 1907, cxx, 31.
[3] Fahr: Heart, 1912, iv, 147. Battaerd: Heart, 1915, vi, 121.
[4] Quart. Jour. Exp. Med., 1911, iv, 289.
[5] Heart, 1912, iii, 343.
[6] Arch. f. d. gesam. Physiol., 1908, cxxiii, 361.
[7] Registrirung des Herzschalls, Berlin, 1911, p. 72.
[8] Ztschr. f. exp. Path. u. Therapie, 1912, xi, 149.

1*B*, *C*, *D*. Records have been taken by direct methods, however, which compare favorably with those of the electrocardiographic curves. Thus, Frank[9] obtained such tracings from dogs by using his segment capsules and Edens,[10] in Fr. Müller's clinic, was able to

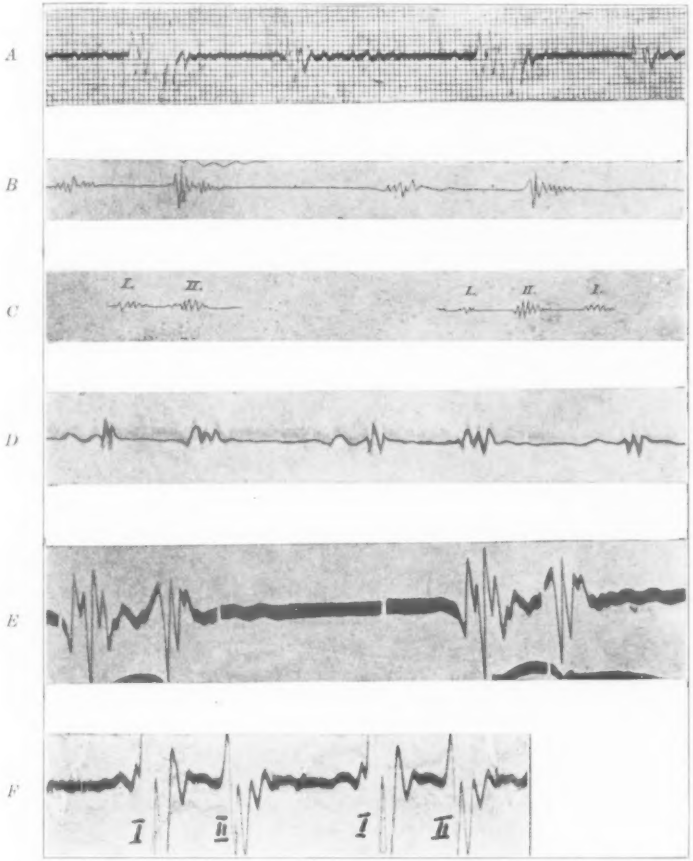


FIG. 1.—Comparison of heart-sound vibrations obtained by Einthoven's microphone method, *A*, compared with records obtained by various direct methods; *B*, curves of Weiss and Joachim; *C*, curves of Gerhartz; *D*, curves of Ohm; *E*, curves of Frank; *F*, curves of Edens.

obtain a few records from selected patients. Photographic copies of these records are also shown in Fig. 1 *E*, *F*.

[9] Ztschr. f. Biol., 1905, xlvi. 524.
[10] Deutsch. Arch. f. klin. Med., 1910, c, Plate II.

When all is said the fact remains that the direct registration of sounds has been used satisfactorily only in selected cases, and when used by the less experienced in routine clinical work has resulted in repeated disappointment or total failure. We have added no new form of apparatus to the already long list of available instruments,[11] but by applying certain principles in the practice of registering sounds have succeeded in successfully recording true sounds in the average routine cases. As far as the Frank capsules are concerned, experience has taught us that failure to record true sounds is not due to the inadequacy of the apparatus, but success is contingent upon attention to certain technical details and upon a constant comprehension of the fundamental guiding principles upon which their use is based. A consideration of the principles and practice of heart-sound registration by direct methods is therefore of current interest.

The Principles of Direct Sound Registration. All methods of direct sound registration endeavor to copy the principle used by the human ear in auscultation. A funnel or stethoscope bell is snugly applied over a cardiac area and the sounds are led by a rubber tube to a capsule covered by a very light membrane. This membrane may be compared to the tympanic membrane of the ear. The conveyed sounds cause both membranes to vibrate. In the case of the ear the vibrations are transmitted by a series of auditory ossicles to the internal ear and are then transformed to nerve impulses registering in the auditory cortex. In the case of the artificial membrane the vibrations are transformed to oscillating light beams, which are photographed on a moving sensitive film.

The Physics of Vibrating Membranes. Since the vibrating membrane constitutes the chief and fundamental part of every sound-recording mechanism it is important to recall a few physical facts applying to such membranes. Every freely swinging membrane if suddenly set in motion continues to vibrate with gradually diminishing amplitude (Fig. 2 *A*) before coming to rest. Such a membrane is called *periodic* and the vibrations are spoken of as the *inherent* or *free* vibrations. The time consumed by each vibration is called the *inherent vibration period* (often designated by $T$), while the number of vibrations it would execute in a second is the *vibration frequency* of a membrane (often designated by $N$). It is obvious that the frequency is the reciprocal of the period $N = \frac{1}{T}$. Hence, we say synonymously that an instrument has a short period or a high frequency. The number of vibrations taking place before complete rest occurs depends on the friction due to damping. If damping is slight, each successive vibration is only slightly diminished in amplitude and a considerable number of free vibrations result (Fig. 2 *A*). On the other hand, if damping is moderately

[11] Wiggers, The Circulation in Health and Disease, Philadelphia, 1915, p. 177.

great, only a few vibrations take place before rest occurs (Fig. 2 *B*). The rate of reduction in amplitude is called the *vibration decrement*. If damping is great enough to prevent all free vibrations the apparatus is called *aperiodic* (Fig. 2 *C*).

Every membrane that has its own tendency to swing may follow imparted vibrations, such as extraneous sounds. It is obvious that no membrane can follow sounds having a frequency greater than

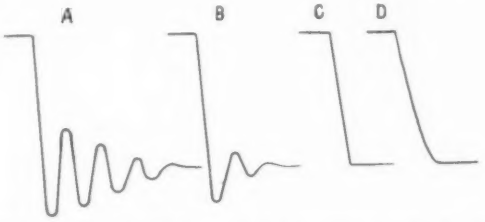


FIG. 2.—Diagrams showing the behavior of a membrane under different damping conditions when a strain is suddenly released. *A*, undamped membrane; *B*, partially damped membrane; *C*, ideally damped membrane; *D*, overdamped membrane.

the inherent period of the instrument. It reacts with maximum vibrations to sounds having the same frequency as the membrane itself, a phenomenon called *resonance*. If a miscellaneous series of waves, equal in amplitude but differing in their periods, are recorded by a membrane whose period is equal to some of these waves, but is greater or less than others, they will not be recorded in equal amplitude. As shown schematically in Fig. 3 the vibrations whose period closely approximates that of the apparatus will appear larger

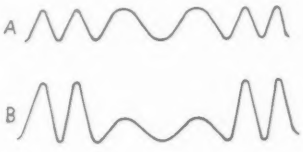


FIG. 3.—Diagram to show the influence of resonance in reproducing sound vibrations. *A*, a theoretical series of vibrations of equal amplitude but varying periods; *B*, record of same by membrane having an inherent period corresponding to the first and last waves.

than those occurring at a rate which is either faster or slower. In recording heart sounds, therefore, it is necessary to employ a membrane whose period is not only as short as but very much less than the shortest oscillation to be recorded.

It is possible for the damping of a membrane to be excessive. When this occurs the membrane is prevented from following the rate of the imparted vibrations accurately; hence, not only is their

contour altered but their amplitude is unduly diminished. On the other hand if a membrane is not aperiodic it has a tendency to add its own vibrations to the imparted vibrations. When it is difficult to produce an optimum damping it is more rational to err slightly toward a periodic system and maintain the apparatus only approximately aperiodic, provided always that the apparatus has an inherent vibration rate well in excess of the oscillations that it records.

Practical Tests to Determine the Efficiency of an Apparatus. An efficient sound-recording system should be so designed that its inherent vibration frequency is not less than 100 and is preferably more than 150 per second; that the decrement of the vibrations is rapid and the sensitiveness of the membrane is so great that 1 mm. of water-presssure in the closed system will deflect the beam of light projected on the camera about 4 cm. By what practical tests can the operator determine whether these conditions are fulfilled?

The vibration frequency may be determined in a number of ways. The method employed by us consists in allowing a periodic membrane which has previously been drawn out of equilibrium to execute its natural vibrations when suddenly released. The simplest means of accomplishing this consists (1) in closing the tube-end commonly connected to the chest receiver; (2) in cautiously creating a slight negative pressure within the system by suction on the side stopcock; (3) in quickly opening the side tube while the paper or film of the photokymograph is running. In this way, as shown in Fig. 5 *E*, a curve is obtained in which each wave decreases by an amount proportionate to its predecessor. Comparison with a simultaneously receded tuning fork curve enables one to figure the vibration period.

A second method suggested by Van Zwaluenberg and Agnew[12] utilizes the principle of resonance. By singing a scale of notes in an even voice into the mouth-piece a series of vibrations for each note can be recorded photographically. Their amplitude will vary, for the membrane responds with the maximal vibrations to the note having the same frequency as the membrane. The difficulty consists in singing sounds of equal intensity. If the loudness of the singing voice changes the amplitude will necessarily vary in proportion.

The decrement of the inherent vibrations depends on the degree of damping. In the Frank capsules no special mechanism for damping exists, but it is unnecessary, and in fact undesirable, as we have experimentally determined. The damping of the air column is materially affected by the relative side opening. The determination of the decrement of such an open system requires special procedures

[12] Loc. cit.

to draw the membrane out of equilibrium. This cannot be carried out satisfactorily without difficulty. A tiny steel splinter may be centrally supported on the membrane and the membrane deflected by an electromagnet, or a light string may be included in the membrane at the time of its manufacture by which the membrane is drawn out. By suddenly demagnetizing the coil in the first instance, or by quickly severing the string, the membrane is thrown into a few damped oscillations. The relative decrease in succeeding vibrations should be great and not more than two or three vibrations should occur.

As a rule an apparatus may be regarded as approximately aperiodic without this special test when the vibrations of the closed system decrease rapidly in amplitude, as shown in Fig. 5 *E* and *F*.

The sensitiveness of the system may be determined by connecting to the rubber tube of the closed system a U-shaped water manometer in which the pressure can be varied slightly by a piece of closed rubber tubing attached to one limb. The excursion of the beam of light when 1 mm. of water-pressure exists in the closed system may be read on the centimeter scale of the camera.

Some Difficulties Attending the Separation of Sound Waves from Mechanical Impacts. When a stethoscope bell is applied over the apex region two sets of pressure variations are transmitted through the connecting tube to the membrane: the one, a rapid set of compressions and rarefactions caused by sound waves, the other, the mechanical variations caused by the apex beat. The latter are so slow that they make no impression upon the ear during auscultation. The recording capsules are sensitive to both disturbances; consequently, if a closed system is used a composite curve of the cardiogram and the superimposed sounds is recorded (Fig. 5 *A*). To annul the grosser mechanical variations the expedient suggested by Einthoven has generally been applied—of introducing a side opening of sufficient size into the system. This expedient introduces a number of interlinking difficulties in direct sound registration. In the first place a more sensitive membrane is required. A membrane that records all sounds in the composite curve yielded by a closed system fails to record the sounds entirely when the side tube is open or, when closure is not sufficient, *registers a number of mechanical variations that may readily be misinterpreted as diminutive sound waves.* This is illustrated in Fig. 5 *B*. These vibrations are due to the fact, shown in the apex curve of Fig. 4 *A*, that at the time of the two heart sounds the variations of the apex beat are peculiarly abrupt and rapid, and hence readily affect less sensitive capsules even when a side leak is introduced. If the apparatus is periodic and its frequency low the impact may inaugurate a series of inherent after-vibrations which, *because they occur at the time when the sounds may be expected to come*, are easily mis-

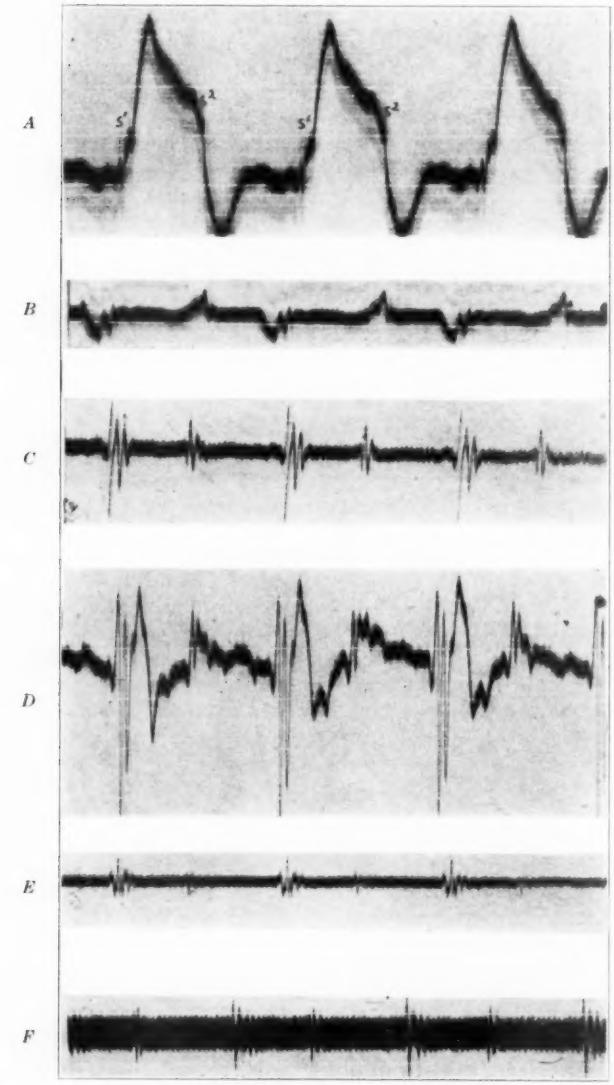


FIG. 4.—Series of records from one individual, illustrating the principles and practice of sound registration. *A*, apex beat with sound vibrations at *S'* and *S''* recorded by a closed system from subject lying on left side; *B*, curve with same apparatus and side tube open. True sound vibrations are absent and remnants of apex curve substituted. These form the basis of pseudo-sounds recorded frequently. *C*, record from same subject by our modified capsules with side tube widely open; *D*, same, with partially closed side opening; *E*, same, with excessive side opening; *F*, same, with wide light band tending to obscure sound vibrations.

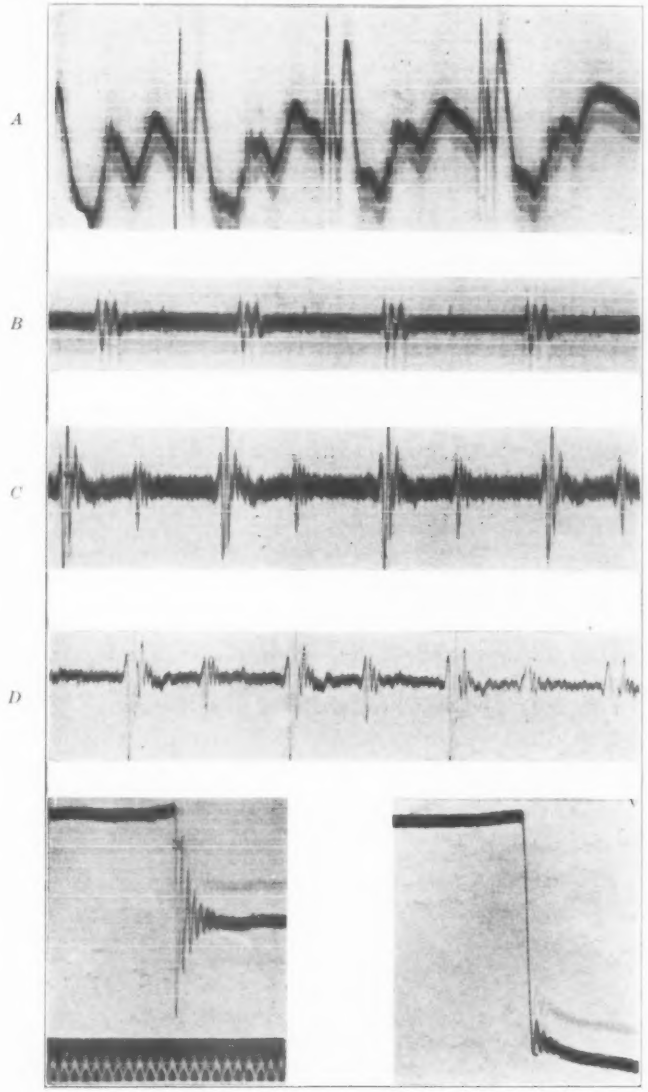


FIG. 5.—*A*, apex curve with same apparatus as used in Fig. 4; *A*, taken with subject in sitting posture; *B*, curve recorded with same apparatus but side tube open; *C*, record from same subject taken by our modified capsules; *D*, more satisfactory record of same due to use of narrower band of light; *E*, curve showing the method of determining the vibration frequency; *F*, curve showing the damping influence of an open side tube.

interpreted as cardiac sounds. This is an error into which many investigators who professed to record sounds by the direct method have been led, as can be seen from a comparison of our spurious sound records in Figs. 4 *B* and 5 *B* with those of Fig. 1 *B, C, D*. It should be distinctly emphasized that the presence of a depression or series of waves at the time when the two sounds may be expected to occur is in itself not a guarantee that they are due to sound vibrations.

This difficulty may be overcome by employing a more sensitive membrane which permits the use of a relatively larger side opening. Curves obtained by such a membrane are shown in Figs. 4 *C* and 5 *C*. Various types of membrane have been suggested, but of all rubber, on account of its stability and elasticity, is probably the best. The thinnest rubber dam commercially available (condom thickness) is too thick to react to sounds from routine clinical cases. By special favor we have succeeded in securing a still thinner variety of rubber dam, but its keeping quality is not good. After considerable experimentation we are able to manufacture our own rubber membrane of a filmy thinness. This is accomplished by drawing the surface of a capsule through a film of rubber cement which has been allowed to thicken somewhat by exposure to the air.

When such a sensitive membrane is employed the difficulty arises that they are responsive to the slightest extraneous noises. The noise of running motors, the hum of fans or tuning-forks, the spoken voice, the walk of the experimenter, the rattle of passing wagons or the gongs of cars are a few of the interfering noises which affect the sensitive membrane, exposed as it is to the air. Furthermore, respiratory sounds, intestinal gurgling, muscular movements of respiration are all liable to be led by the tubing to affect the membrane from the inside. Unlike the human ear, which can be trained to mentally exclude sounds it chooses not to hear, these capsules are not selective but record all vibrations. Although satisfactory means have not been suggested to obviate all these vibrations, very satisfactory records can be obtained by operating the apparatus in a not too quiet room, as shown in Figs. 4 *C* and 5 *C, D*. Recently it has become possible to materially reduce in number the accidental-room vibrations. This was accomplished by inclosing the membrane in a housing with a glass window, thus preventing the impingement of accidental room-vibrations (*cf.* February issue of *Am. Jour. of Physiol.*, 1917). These records have one advantage over the phonocardiographic curves of Einthorn, *i. e.*, they do not add adventitious vibrations due to the readjustment of carbon particles in the microphone, such as often causes trouble when even a moderately strong current passes.

It is frequently difficult to determine the optimum side opening. The degree of opening required depends on the sensitiveness of the membrane and on the relative intensity of the sounds and apex

variation. If the opening is insufficient the sound curve is partly deformed by an element of apex curve, as shown in Fig. 4 *D*. If the opening is too large the smaller vibrations may fail to be recorded (Fig. 4 *E*) and occasionally the second sound may be entirely absent. When the second sound is soft and the first accentuated it may be very difficult to obtain a record which does not show some distortion due to the apex curve and still records the second sound satisfactorily. In practice it is therefore usually desirable to record a series of sound tracings with different side openings. The first tracing is taken with the side opening so adjusted that *two sets* of oscillations are clearly visible in the projected band of light. A second and third record are subsequently taken with a greater and less degree of closure respectively. By comparing the three curves all the sound components can be satisfactorily established.

THE APPARATUS AND TECHNIC IN RECORDING HEART SOUNDS. *The Sound-recording System.* In recording heart sounds a communicating system, consisting essentially of a receiver, rubber tubing, and a Frank segment capsule, transforming the sound vibrations into oscillations of a beam of light, is utilized. The receiver found to give the best results is an open one, though not of the type of any of the numerous models of stethoscope bells. It is of brass and 9 cm. in diameter, which is somewhat larger than most of the more popular stethoscope bells. This point is quite important in recording heart sounds, for less perfect results were obtained when receivers built to the same scale but covering smaller areas of chest wall were used. A firm and immovable apposition between the chest wall and the receiver is essential. A very considerable increase in amplitude and clearness of the sounds often occurs when the receiver is merely pressed more firmly to the chest. A simple means of obtaining the desired apposition is afforded by strapping an elastic belt around the chest. This presses the open aspect of the receiver against the chest when the tubular transmitting part is fitted through a hole in the belt fabric.

It is not desirable to record heart sounds through a receiver held away from the chest wall. The sounds heard over different cardiac areas and attributed to the heart in reality are merely vibrations of the chest wall and are therefore best recorded by direct contact. In addition, without direct contact of the receiver, a very delicate registering system must be used which has the drawback that many extraneous vibrations are recorded. The clarity of the sound-records, just as that of the usual stethoscopic auscultation, is diminished by such factors as excessive fat, a large breast, emphysema, etc.

Although an apex beat that corresponds more definitely with the position changes of the heart is obtained when the subject lies on the left side (*cf.* Figs. 4 *A* and 5 *A*), the sounds are recorded more readily in the sitting posture. A comparison of Figs. 4 *C* and 5 *C*.

shows that more vibrations are recorded in the latter posture. This is probably due to the damping of the chest vibrations by the bedding.

The rubber tubing which leads from the receiver is soft and flexible, 5 mm. in diameter and not more than 70 cm. long. It is supported from above at a short distance from the chest by a long, lax, spiral spring, giving to the tube when in motion a very low vibration frequency. The delay in transmission was found to be 0.0027 second, a negligible time interval for ordinary purposes.

The Frank capsule supported upon the miniature cannon carriage, as previously described by one of us,[13] is used as the recording mechanism. There is a difference in that the material composing the membrane is an extremely thin film of rubber prepared as follows: A glass tube is withdrawn from a jar of rubber cement and a drawn-out band of cement is formed by tilting the rod toward

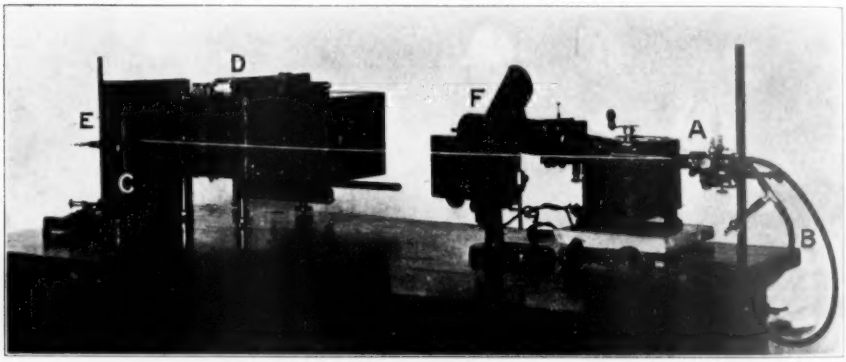


FIG. 6.—Photograph showing how two sound capsules may be aligned at right angles to a galvanometer projection. Description in text.

the horizontal plane. The open end of the segment capsule is now passed through this cement at right angles to the band. A thin film of uniform thickness will adhere to the edges and cover over the opening. After the rubber cement has nearly hardened the mirror is put in place so that it pivots upon the cord side. Care must be taken that the entire back surface of the mirror adheres. The mirrors used are very tiny, measuring 1.5 mm. by 2 mm., and weighing 0.2 mg. Obviously, they add but little effective mass to the delicate recording system.

In order that simultaneous tracings of the apex beat, supraclavicular venous pulse, or heart sounds from a different cardiac area may be taken, a second Frank capsule is attached to and horizontally aligned with the first capsule (Fig. 6). The type of

[13] Wiggers: Jour. Am. Med. Assn., 1915, lxiv, 1305.

membrane employed with the second capsule depends entirely upon the type of vibration to be recorded. The reasons for this have been detailed above. Suffice it to say that for coarser variations, such as the apex beat, light rubber dam is used, while for heart sounds the thinnest rubber cement film is made.

*The Projection and Photographic System.* With the capsules horizontally aligned a common beam of light is projected upon both. The capsules are so close together that the error in projection cannot be measured when the speed of the recording paper does not exceed 50 mm. per second. The most satisfactory source of the light beam has been a 5-ampère automatic arc lamp. The diverging rays radiating from the crater of the positive carbon pass through a lens which renders them parallel. These parallel rays in turn are cut down from above and below by an adjustable slot so that only a horizontal band of light emerges. Precision in focusing this band is accomplished by a final lens which focuses the positive carbon about 3 cm. in front of the capsule mirrors. Care must be exercised not only with the focus but also with the width of the light band. By comparing Figs. 5 *C* and 5 *D* it is seen how much to be preferred is the narrow light; in fact, it is possible for the sound oscillations to be less in amplitude than the width of a wide light band (*cf.* Figs. 4 *E* and *F*). In such a case the more delicate features are lost. The oscillations are recorded photographically by playing the vertically oscillating beam of light, as reflected from the mirror of the segment capsule, upon bromide paper moving horizontally at the uniform rate of 40 to 50 mm. per second.

When the electrocardiogram is simultaneously recorded it is essential that the arc lamp used for the capsules be in a position not parallel with the magnetic field of the galvanometer. This requirement precludes the possibility of throwing the three light beams directly upon the photographic paper. Either the two capsule beams or the light from the galvanometer must be deflected at an angle of precisely 90 degrees before passing into the photokymograph in order that a vertical alignment of the different records be preserved. For experimental convenience we deflect the galvanometer light.

It is probable that most workers having their galvanometer aligned with the photokymograph will prefer to deflect the capsule beams. The alignment for such an arrangement is shown in Fig. 6. The source of light is the arc lamp *F*. The light beam may be seen as it is projected upon the mirrors of the segment capsules *A*. Thence the rays are reflected upon the mirror *C*, which deflects them through an angle of 90 degrees into the slot of the photokymograph *D*. The light beam from the galvanometer is indicated by the string *E* as passing above the deflecting mirror directly into the photokymograph. Since this photographic arrangement requires vertical movements of the galvanometer string which actually moves

horizontally in its vertical suspension all of the rays emerging from the projection ocular of the galvanometer are rotated horizontally by a series of quartz prisms. If it is desirable to use a kymograph in which the paper film moves vertically it is merely necessary to arrange the capsules so that the mirrors of the segment capsules tilt in the same *vertical plane* and that a vertical instead of a horizontal band of light is projected upon them.

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## THE METABOLISM AND TREATMENT OF RHEUMATOID ARTHRITIS. FOURTH PAPER.

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In three previous communications,[1] the writer has presented a series of 37 cases of rheumatoid arthritis in which certain laboratory and clinical findings were made the basis of a method of treatment. The method in question consists essentially in the curtailment of diet, particularly the carbohydrates and proteins, to a point of tolerance which varies with the individual. In the last studies, experiments were reported, among other data, in which it had been apparently possible to induce exacerbations, in patients previously rendered free from the disease, by the feeding of pure carbohydrate.

The present article concerns further evidence in regard to the carbohydrates and, more particularly, evidence as to the role played by the fats; together with certain other findings. A series of 11 cases is therefore presented for the purpose of illustrating dietary experiments. No cases are here reported for the single purpose of illustrating further the therapeutic effect of a reduced diet alone, although such are available, as this has been done elsewhere.[2]

The plan has been followed here, in general, of determining the customary caloric intake of the individual as a help in ascertaining the reduction in food required, as elsewhere mentioned.[3]

From the caloric intake thus determined the respective proportions of protein, carbohydrate and fat could be approximated; in some cases very closely. In nearly all cases the diets which were followed, even the unrestricted "House Diet," were prepared according to fixed formulæ in which the above proportions are definitely known.[4]

[1] The Metabolism and Successful Treatment of Chronic Joint Disease; A Preliminary Report, Am. Jour. Med. Sc., October, 1912, No. 4, cxliv, 744; The Metabolism, Prevention, and Successful Treatment of Rheumatoid Arthritis; Second Contribution, ibid., December, 1913, No. 6, cxlvi, 895; January, 1914, No. 1, cxlvii, 111; February, 1914, No. 2, p. 265; March, 1914, No. 3, p. 423; The Metabolism and Treatment of Rheumatoid Arthritis, third paper, Am. Jour. Med. Sc., March, 1916, No. 3, cli, 351.

[2] Loc. cit.

[3] Loc. cit., number ii.

[4] Edwin A. Locke: Food Values.

In making the calculations of the proportions of carbohydrate, protein and fat in the ingested food, discrepancies sometimes occur between the caloric totals thus obtained and those calculated for the diet as a whole. These discrepancies are due to the omission from calculations of such foods as spinach, bouillon, lettuce and the like whose totals do not in these cases importantly influence the relative percentages. It will be seen that in the probationary diets and in the therapeutic diets, the proportions of the three ingredients, protein, carbohydrate and fat are practically always in such striking contrast that these discrepancies are negligible. Where more refined experiments could be conducted, these figures are exactly obtained, as in Case XLVIII.

In all of these cases, sources of possible infection had been removed before treatment was begun and all were examined for these by *x*-rays of teeth, sinuses, etc., by nose and throat specialists, by dentists, etc. In Cases XLIII, XLIV, XLV tonsillectomy was performed, on advice of the writer before considering dietary treatment.

The diagnosis of arthritis was corroborated in every case by *x*-ray pictures, taken mostly by Dr. William S. Newcomet, to whom the writer desires to express his appreciation.

Limitations of space preclude all but the barest outlines of the following cases except where a particular point is illustrated.

Case XXXVIII.—Mrs. S., aged about fifty years, referred by the courtesy of Dr. Hamilton Levings, of Milwaukee, was admitted May 18 and discharged July 3, 1916. The patient had a life-long tendency to "rheumatism" and presented a diffuse arthritis of three years' duration. There were very little soft tissue involvement and few objective signs of arthritis, and the condition seemed to concern largely the tendons. Unsuccessful attempts were made, analogous to those to be described later, under other cases, to replace the carbohydrate largely by fat, but her digestion was unequal to the task. After various reductions and fluctuations the diet was finally reduced for a few days to a mixed[5] one of 670 calories which was followed by distinct subjective improvement everywhere, but the patient could not be maintained on such a low intake. The diet was then increased to about 1000 calories, together with cod-liver oil, and this was followed with benefit though it seems plain that this case gave a definite but only limited response. During a period of unrestricted diet lasting six weeks she grew worse, developing effusion in the capsules of the finger-joints and improved, within limits, with subsidence of the effusion when the diet was again among reduced to about 1300 calories. It is perhaps safest to include this case among those instances which clinically fail to be benefited.

[5] By a mixed diet is meant one containing protein and fat in approximately the usual ratios, and carbohydrate in rather less than the usual ratio for the total caloric value as described in paper No. 3.

Case XXXIX.—Mrs. R., aged about fifty-seven years, and referred by the courtesy of Dr. John W. Thornton, of Wheeling, W. Va., was admitted October 15, 1915 and discharged June 3, 1916. She was a wheel-chair invalid, with muscular wasting, secondary to widespread arthritis of seven years' duration involving nearly all joints and it was long doubtful whether dietary treatment could justifiably be attempted. This case is detailed chiefly because of observations on the urine to be mentioned later. The probationary house diet yielded about 2500 calories and on November 17, 1915, she was given a mixed diet yielding about 1400 calories, of which about 400 calories came from carbohydrates, about 200 came from protein, and about 800 came from fat. Almost at once this patient showed great improvement, felt less pain and the swelling of her hands progressively subsided. A difficulty of treatment presented in her easily disturbed digestion and the necessity of keeping up her general strength and weight in view of her invalidism. Because of this her diet was frequently interrupted and it was never possible to push it vigorously.

A *résumé* of this case in April, 1917, reveals the unmistakable influence of diet in an advanced case as shown by some return of function and decrease in swelling and pain. This case is still under observation and interpretation of the end result, as limited by the above factors, must be guarded but the arthritis *per se* falls unmistakably among the types susceptible of great benefit by these measures.

Case XL.—Mrs. X., aged about fifty-eight years, referred by the courtesy of Dr. Frank B. Mitchell, of East Orange, N. J., was admitted April 12 and discharged June 3, 1916. She presented muscular pains together with an arthritis of practically all the joints of the hands. A probationary house diet yielded about 2500 calories per diem, of which about 1020 came from carbohydrates, 586 from protein, and about 633 came from fat. An attempt to feed this patient a large amount of fat was unsuccessful because of gastric indigestion, but after several modifications her diet on May 7, 1916, yielded about 1589 calories, of which about 376 came from carbohydrates, 153 from protein, and 819 from fat. This diet distinctly benefited her, but owing to her impatience the fat was first reduced, fo'lowed by reduction of the carbohydrate and protein until she was taking on May 26 about 1111 calories of a mixed diet.

On May 27 nearly every sore-point in her hands and elsewhere had improved and many had disappeared.

On June 3, the patient left the hospital prematurely against advice. Before beginning treatment her weight was increased 5 pounds by forced feeding, and on leaving the hospital it was exactly the same as upon admission.

Case XLI.—Mary B., aged twenty-nine years, a ward case, admitted April 19, 1915, and discharged January 6, 1916, had a

diffuse arthritis of three years' duration incapacitating her. A reduced mixed diet of 1078 calories determined as in the other cases resulted in definite but limited improvement with loss of weight. After forced feeding and a large gain in weight she was given a diet of 1707 calories supplied by 300 grams of graham crackers, three apples, 21 grams of sugar and 5 grams of butter per diem. Practically all of the caloric value of this diet except for 120 calories was afforded by carbohydrates and she remained in active arthritis.

On December 30, 1915, this diet was changed to one yielding 1440 calories, of which about 1016 came from fat about 30 came from protein and about 378 from carbohydrate distributed as follows: Graham crackers 60 grams, 3 apples, 150 grams each, 30 grams of butter, olive oil 90 c.c.

On January 6, 1916, she insisted on leaving the hospital but applied for readmission in two days. She felt apparently quite well on leaving and on January 5 and 6 had walked considerably and freely. The objective evidence of improvement was subsidence of a fibrous nodule on the right ring finger and subsidence of the soft tissue involvement of most of the small joints. What the end-result might have been in this case cannot be prognosticated but there is no doubt as to the beneficial changes witnessed in the short period last indicated.[6]

Case XLII.—Miss C. M., aged fifty-six years, referred by the courtesy of Dr. John H. Musser, Jr., was admitted April 28, and discharged June 20, 1916. She had suffered from "rheumatism" for forty years. For five years the hands had been progressively involved and of late the knees and feet. On the house diet she ingested about 1581 calories a day of which about 851 calories came from carbohydrates, 323 from fat and 173 from protein.

On May 7, 1916, the patient was put upon a mixed diet yielding 1720 calories of which about 402 came from carbohydrates, about 183 from protein and about 1024 from fat. Thus the proportions of carbohydrates, and fat were almost reversed. After insufficient progress, on May 23 oil and butter amounting to 643 calories in all were removed from her diet, leaving a balance of 1077.

On May 26, 1916, there was some improvement, but as she was restless and impatient the diet was further changed by removing carbohydrate and protein to the extent of 227 calories, leaving about 850 calories. There was marked improvement and on June 4 she was holding her weight surprisingly well. The diet was then reduced to approximately 700 calories, and on June 7 she was better than at any time previously there being no objective sign of inflammation anywhere.

On June 20 her condition was so much improved that she felt she could follow her profession as a piano teacher. This patient was

[6] This patient was under observation only at the early and late periods of her stay in the Hospital.

seen by Dr. Musser on May 31 and June 13. Under protest she was allowed to follow this diet for a limited period at home under the supervision of the Social Service and was given cod-liver oil. Because of conditions at home she was unable to lead the quiet life advised and shortly had to be placed upon a larger dietary by Dr. Musser. This patient showed response to diet and became largely though not entirely free from symptoms while in the hospital where her weight fell from 128½ to 120 pounds. The end clinical result to her was *nil*.

CASE XLIII.—Mrs. N., aged about sixty-four years, referred by the courtesy of Dr. Horace Jenks, was admitted May 20 and discharged June 24, 1916.

This patient suffered from an arthritis of thirty years' duration involving nearly every joint. Tonsillectomy had been of no avail. On the probationary house diet she ingested about 1800 calories per diem which were afforded in the proportion of about 600 from carbohydrate, 333 from protein and about 700 from fat.

On May 26 she was given a mixed diet of about 1800 calories of which about 407 came from carbohydrates about 183 came from protein and about 1200 came from fat.

On June 1, improvement was noted but not knowing whether the fats were delaying progress 484 calories derived from olive oil were removed bringing the caloric total down to about 1334. Her progress was steady and on June 24 the sciatica and nearly all the tender spots in the hands had cleared up. She had had almost daily headache which disappeared entirely. The improvement in this case was beyond question, and the only real difficulty was in controlling her daily life. In the hospital her weight fell from 148 to 140 pounds. It is suggested that this might have been avoided by continuing the large fat intake and devoting more time to convalescence.

CASE XLIV.—Miss D. H., aged about forty and referred by the courtesy of Dr. John H. Girvin, was admitted March 25 and discharged June 29, 1916.

The patient suffered from arthritis of five years' duration involving the shoulders and knees, and the right elbow which could not be flexed beyond a right angle. On the probationary house diet she ingested about 1700 calories daily of which about 1026 came from carbohydrates, about 380 from protein and about 300 from fat.

On April 12, 1916, she was placed upon a mixed diet yielding about 1850 calories derived in the proportions of about 402 from carbohydrates, 118 from protein and 1318 from fat. The proportions of carbohydrates and fat were thus essentially reversed, the meat protein was reduced about 60 per cent. and the total calories were increased.

On May 1 the patient had made distinct though limited progress, best evidenced by less general soreness and increase of function at the right elbow which moved more freely than for five months

previously. She followed this diet religiously and in April, 1917, the situation could be summed up as follows: Periods of discomfort lasting for some days would be followed by weeks of bienaise in which she would be nearly free from all pain or stiffness. The periods of exaccerbation were marked by much less severe pain than she had suffered nearly constantly before treatment; and since treatment was begun the function of her right elbow had slowly but steadily increased. Particularly at night had pain been substantially modified and while she was not well it was clear that she had made unmistakable progress. During treatment the patient was given cod-liver oil. On admission and on discharge from the hospital she had a distinct secondary anemia, but in October, 1916, her blood count was normal. While in the hospital on the diet her weight fell from 114 to 105 pounds, from which it climbed to 112 pounds in January, 1917.[7]

Case XLV.—Mrs. M. W., aged about thirty-eight, referred by the courtesy of Dr. H. R. Wharton, was admitted January 24 and discharged June 26, 1916. This patient was anemic and suffered from a violent arthritis of about nine months' duration involving hands, knees and feet. Upon a probationary house diet the patient ingested about 2000 calories per diem yielded in the proportions of about 400 calories from protein, 1140 from carbohydrates and 602 from fat. On April 19, 1916, she was placed upon a mixed diet yielding about 2100 calories, of which about 488 came from carbohydrates, 233 from protein and 1400 from fat. The proteins were thus reduced about 50 per cent., the carbohydrates about 60 per cent. and the fats increased by about 100 per cent. A distinct improvement was noticeable, which with fluctuations continued until June 1, when it became less obvious. As a test of the value of fat, the bread in her diet was reduced by 60 grams a day which cut the caloric total down to about 1940.

On June 8 there was distinct improvement and the fingers changed their shape because of subsidence of inflammation. Although the evidence was not complete it strongly suggested that fat was the least harmful of the three dietary ingredients in this case. The loss of weight in the hospital was from 118 to 113 pounds. Improvement was maintained in January, 1917, as reported by letter.

Case XLVI.—Mrs. S., aged about fifty-two years, referred by the courtesy of Dr. S. McC. Hamill presented an arthritis of several years' duration involving all terminal finger phalanges. During the probationary diet she ingested an average of about 1723 calories, of which roughly 1000 calories came from carbohydrates, 400 from protein, and 275 from fat. She was then placed upon a mixed diet yielding about 1800 calories of which about 450 came from carbohydrates, 150 from protein and 1200 from fat.

[7] This case illustrates the time sometimes required for benefit to become established and also the importance of maintaining conditions invariable in such instances.

The figures in this case are not as accurate as in cases treated at the hospital as she weighed her food herself, under instruction but the respective proportions of the three food ingredients are correctly represented. She improved from the start and in two months all tender points were greatly improved and most of them had disappeared. The subsequent control of this patient was not satisfactory and she later disappeared from observation. Her loss of weight was from 225 to 205 pounds. She was seen by Dr. Hamill in June, 1916.

Case XLVII.—Miss M. S., aged about fifty years, referred by courtesy of Dr. Stewart Rodman, was admitted November 2, and discharged November 18, 1916. This case warrants greater detail and presented an arthritis of knees, hands, and jaws, with pain in muscle groups, dating back five years. On the probationary house diet she ingested about 2400 calories of which about 1200 came from carbohydrates, 215 from protein and about 900 from fat, leaving a small difference attributable to unreckoned calories from spinach, soup, etc.

On November 13th, she was put upon a mixed diet yielding about 2450 calories of which about 588 came from carbohydrates, 130 from protein and 1719 from fat. Benefit from this dietary was unmistakable and most gratifying. She progressed steadily and on December 17 was relieved of about 85 per cent. of her original symptoms. In fact, whereas she walked previously with much difficulty, could not get down upon her knees, etc., she was then walking as much as two miles a day with entire comfort. She still had occasional symptoms such as stiff neck in the early morning which would last for half a day, or a temporary exaccerbation in one joint, but only one conclusion was possible as to her general condition. A most interesting feature is the fact that in the period during which she followed the therapeutic diet her weight rose from 113½ to 116½ pounds a clear gain of 3 pounds. This was the first instance in which this has occurred in the writer's experience. This experiment shows not only that fat may sometimes be very well borne by these cases; and that in view of the reversal of the proportions of carbohydrate and fat in this case the harmful role of the carbohydrate becomes additionally evident; but it shows also that in selected instances it is possible adequately to maintain nutrition or achieve a gain in weight while the harmful elements in the diet are eliminated; no fat absorption experiment was performed but the stools showed no gross evidence of free oil. The gain in weight is substantial evidence of large, if not complete utilization of the ingested fat.

Case XLVIII.—Miss M. C., aged twenty-two years, referred by the courtesy of Dr. James E. Talley, was admitted November 12, 1916, and presented an arthritis of three years' duration involving the ankles, hands and wrists. This case was of great interest and yielded definite experimental data. The patient had been thoroughly examined for infectious foci and tonsils and several teeth had been

removed without improvement e ght months earlier. The probationary house diet yielded 1370 calories. On December 10 she was placed upon a diet of 1396 calories, consisting of 334 grams of graham crackers and 10 grams of butter per diem, of which about 924 calories came from carbohydrates, 123 came from protein and about 349 came from fat.

On December 20 she was worse and had lost 1½ pounds.

On December 21 the experiment was started of greatly reducing her carbohydrates, keeping the protein about the same and increasing the fat to make the total caloric intake as high as before. Obviously if she improved on this diet it would indicate that the fat could be well borne and, further, that the carbohydrates were harmful. She was therefore started upon a diet consisting of 136 grams of graham crackers, 5 tablespoonsful of olive oil and 30 grams of butter per diem yielding about 1423 calories.

On December 24 there was distinct improvement but on December 27 she was still losing weight. In reducing the graham crackers from 308 to 136 grams the protein had been reduced by about 17 grams. In order to make up this protein deficit as a possible cause of improvement she was given three eggs a day in addition which yielded about 20 grams of protein and about 18 grams of fat making an increased total caloric value of 1675, of which about 408 calories came from carbohydrates, 135 from protein and 1132 from fat, total 1675. This was more in calories than she ingested on the house diet. There was no gross evidence of free fat in her stools and as evidence of the degree to which she had utilized the fat of her food can be mentioned her weight which rose upon this last diet from about 90 to 94 pounds.

On February 7, 1917, she was 95 per cent. relieved of all true arthritic symptoms, could walk well and close her hands well. There was distinct dimpling over all of the previously inflamed phalangeal joints, which were not tender to pressure, about the only remaining symptom being some pain on lateral motion of one foot which was pronated and rigid from faulty mechanics but had nevertheless shared the great improvement.[8]

In the work last reported attention was called to the fact that contemporaneously with natural or induced exaccerbations of the disease there seems to be a tendency for the urine to show a decreased acidity as measured by the hydrogen-ion concentration. The statement was also made that these findings needed corroboration for a longer series before they could be accepted as established. These observations have now been extended and it may be said that whereas this tendency toward a decreased acidity seems to be present in some cases, it is by no means always so. It apparently bears no necessary relation to subjective exaccerbations alone.

[8] Condition excellent, and weight 97½ pounds on April 19, 1917.

Observations on the hydrogen-ion concentration were made for long periods in Cases XLI, XLIV, XL, XLII, XLVI, XLV, XXXIX, and XLIII but significant changes were observed in two only and in one case notably, XLIV, the hydrogen-ion concentration maintained a surprising concentration throughout notwithstanding marked fluctuations in the subjective sensations. None of these cases showed any striking objective fluctuations, etc., which may explain this constancy.[9] The cases above examined were all upon fixed and constant diets. With the idea of obtaining some picture of the metabolism as a whole at the time of an exaccerbation accompained by a drop in urinary acidity certain observations were conducted in Cases XXXIX and XLV. The results are given in the following figures. The hydrogen-ion concentration was determined according to the methods of Palmer & Henderson.[10]

The ammonia was determined by Folin's method, the nitrogen by the Kjeldahl method, the total acidity of the method of Adler and Blake[11] and the uric acid by the Folin-Shaffer method.

CASE XXXIX.

| | PH | $NH_3$ | $NH_3$ N. as per cent. of total N. | N. | |
|---|---|---|---|---|---|
| Jan. 11 | 6.15 | .. | .. | .. | Well. |
| 12 | 6.15 | 0.2883 | 6.45 | 3.6803 | Well. |
| 13 | 6.7 | 0.1958 | 4.11 | 3.9084 | Sick. |
| 14 | 6.5 | 0.2082 | 4.7 | 3.7142 | Well. |
| 15 | 6.5 | 0.1763 | 4.14 | 3.5078 | Well. |
| 16 | 6.3 | 0.1926 | 4.62 | 3.4362 | Well. |
| 17 | 6.5 | 0.2633 | 6.28 | 3.4437 | Well. |
| 18 | 6.85 | 0.1905 | 4.36 | 3.5959 | Sick. |
| 19 | 6.7 | 0.1922 | 4.21 | 3.7585 | Better. |
| 20 | 6.7 | 0.1926 | 4.36 | 3.6382 | Better. |
| 21 | 6.15 | 0.2758 | 6.15 | 3.6909 | Gastro-intestinal disturbance, joints pretty well, however. |

It will be seen from the figures that in each case they reflect a drop in the hydrogen-ion concentration contemporaneously with the exaccerbation; this occurring twice in each case during the period of observation. In Case XXXIX the ammonia curve followed

[9] The drop in acidity may be referable to conditions accompanying effusion or other results of inflammatory processes.

[10] Walter W. Palmer, Lawrence J. Henderson: Clinical Studies of Acid Base Equilibrium and the Nature of Acidosis, Arch. Int. Med., August, 1913, xii, 153–170. The notation used signifies the logarithm of that number which expresses the actual acidity in terms of hydrogen-ion concentration; the logarithm decreases as the acidity increases and *vice versa* and the minus sign is omitted. It should be here stated that the logarithmic figures do not portray graphically the differences in reaction of the urine, as a drop from No. 7 to No. 4 in the scale of eleven flasks, three members of the series, is indicated merely by the change from 6 to 7 in the logarithm.

[11] Arch. Int. Med., 1911, vii, 479.

in general that of the hydrogen-ion concentration. The nitrogen behaved oppositely rising where the others fell and *vice versa*. In Case XLV much the same situation obtained; the total acidity and uric acid also following in general the curve of acidity.

CASE XLV.

| | Ph. | $NH_2$ | $NH_2$ N. as per ct. of total N. | Total acidity. | N | Uric acid. | |
|---|---|---|---|---|---|---|---|
| April 22 | 6.3 | | | | | | Well. |
| 23 | 6.5 | | | | | | Well. |
| 24 (1870 c.c.) | 6.15 | 0.2034 | 3.2 | 269.2c.c. $\frac{1}{10}$ N.HCl | 5.2360 | 0.2138 | Well. |
| 25 (2050 c.c.) | 6.85 | 0.1952 | 3.055 | 176.4 | 5.2508 | 0.1576 | Exacerbation. |
| 26 (1930 c.c.) | 7.0 | 0.2362 | 3.667 | 206.5 | 5.2959 | 0.1483 | Still sore. |
| 27 (1980 c.c.) | 6.85 | 0.2154 | 2.961 | 186.0 | 5.9875 | 0.1141 | About the same or slightly better. |
| 28 (1880 c.c.) | 6.85 | 0.2045 | 3.068 | 176.9 | 5.4745 | 0.1178 | About the same. |
| 29 (1615 c.c.) | 6.5 | 0.2196 | 3.609 | 226.0 | 4.8837 | 0.1846 | Better; less pain everywhere. |
| 30 (1695 c.c.) | 6.4 | 0.2305 | 3.844 | 254.1 | 4.9358 | 0.1938 | Better. |
| May 1 (1635 c.c.) | 6.5 | 0.2001 | 3.228 | 256.6 | 5.1274 | 0.1349 | Feels pretty well. |
| 2 (1800 c.c.) | 6.85 | 0.1958 | 3.263 | 142.2 | 4.9392 | 0.2295 | Very well. Drop unaccounted for |
| 3 (1534 c.c.) | 6.5 | .. | .. | .. | .. | .. | Stomachslightly upset but feels pretty well as to joints. |
| 4 | 6.5 | .. | .. | .. | .. | .. | Well. |
| 5 | 6.2 | .. | .. | .. | .. | .. | Well. |
| 6 | 6.85 | .. | .. | .. | .. | .. | Exacerbation. |
| 7 | 6.85 | .. | .. | .. | .. | .. | Exacerbation. |

In Case XLII it was noteworthy that she withstood remarkably well the several low diets upon which she was placed holding her weight surprisingly as have other cases previously mentioned and in order to obtain a reflection of her nitrogen loss, a nitrogen balance experiment was performed upon her when she was taking a mixed diet of about 700 calories per diem as per the appended case history but it reflected nothing out of the ordinary. In seven days her nitrogen balance was as follows: Nitrogen outgo, 21.99; nitrogen intake, 16.87; nitrogen loss (urinary), 5.04.

In view of the experiments previously reported in which it was apparently possible to induce exaccerbations in cases of rheumatoid arthritis, previously rendered free or nearly so from symptoms, by the ingestion of cane sugar, experiments were conducted upon the carbondioxide tension of the alveolar air in a series of normal and diseased subjects with the idea of determining any marked abnor-

mality in the rate or degree of utilization of carbohydrate by the diseased subject. Four control cases and five diseased subjects were studied two of the latter being in active arthritis and three of them well. The plan of procedure was to determine the carbon dioxide tension in the early morning upon an empty stomach, then to feed pure carbohydrate in the form of cane sugar in amounts varying from about 200 to 300 grams according to the capacity of the individual and then to watch the carbon dioxide tension at intervals of about twenty minutes throughout its rise and until it had returned to normal. This whole procedure occupied at least five hours and sometimes eight. The method used was the Plesch method as previously reported.[12] In addition some observations were made with the Haldane method using a valve, somewhat as suggested by Boothby and Peabody.[13]

In general the former method was the more dependable of the two. It was found in working with clinical subjects, especially beginning upon a fasting stomach, that the reliability of the determinations was influenced by the fatigue of the patient even when the latter was accustomed by repetition to the experiments. The aberent figures occasionally introduced were sometimes as widely fluctuating as those due to the rise in carbon dioxide tension and care was necessary to avoid misinterpreting them.

A series of 26 experiments was carried through *in toto*, some being repeated on the same subject. In some subjects consecutive uniformity was impossible. The following figures are from a normal case and one in active arthritis respectively:

| Normal Case A. F., Nov. 11, 1916: | | Case XLVIII, Active Arthritis, Nov. 30, 1916: | |
|---|---|---|---|
| Before sugar: | | Before sugar: | |
| 10.10 A.M. | 45.806 M.M. $CO_2$ | 8.45 A.M. | 34.361 M.M. $CO_2$ |
| 10.20 " | 44.299 " " | 9.5 " | 33.649 " " |
| 10.41 " | 45.445 " " | 9.30 " | 35.499 " " |
| 10.57 " | 44.650 " " | | |
| 11.46 " | started sugar 287 gms. | 10.4 " | started sugar 234 gms. |
| After sugar: | | After sugar: | |
| 12.30 P.M. | 45.096 M.M. $CO_2$ | 10.40 A.M. | 36.175 M.M. $CO_2$ |
| 12.55 " | 44.156 " " | 10.50 " | 34.327 " " |
| 1.42 " | 44.879 " " | 11.00 " | 35.109 " " |
| 2.20 " | 47.698 " " | 11.25 " | 35.602 " " |
| 2.45 " | 46.180 " " | 11.40 " | 38.663 " " |
| 3.00 " | 50.213 " " | 12.00 M. | 34.043 " " |
| 3.20 " | 46.890 " " | 12.15 P.M. | 36.175 " " |
| 3.40 " | 47.107 " " | 12.50 " | 34.683 " " |
| 3.55 " | 45.589 " " | 1.20 " | 34.374 " " |
| 4.15 " | 45.289 " " | 1.45 " | 35.368 " " |
| | | 2.10 " | 34.019 " " |

Inspection of the figures shows that no immediate difference in the effects of large amounts of pure carbohydrate when ingested by

[12] The Metabolism and Treatment of Rheumatoid Arthritis, third paper.

[13] A Comparison of Methods of Obtaining Alveolar Air, Arch. Int. Med., March, 1914, xiii, 497–506.

normal and by diseased subjects is reflected in the carbon dioxide tension, at least under the conditions of experiment.

It is a pleasure to acknowledge the assistance of Miss E. C. Titlow in making the observations on alveolar air.

Discussion. Consideration of the above cases reveals some interesting points. In the first place it is clear that the ingestion of fat by arthritic cases treated in the above manner may result differently from the ingestion of carbohydrates. It has appeared from a study of the present series that fat could be ingested with benefit in larger amounts than could carbohydrate but it has remained for the last two quoted experiments to indicate this definitely. In two cases where a large amount of carbohydrate was ingested during a period in which the patient remained ill, this amount of carbohydrate was reduced by approximately two-thirds and then replaced entirely by fat. In one of these cases the protein intake was increased with the increase of fat and in the other it was somewhat reduced. Coincidentally with this change in diet there occurred in each case an amelioration of symptoms which was beyond all question and in sharp contrast to the preceding condition of health. It is of the highest interest to note that each of these cases gained weight. It might be alleged that whereas reduction of carbohydrate had been beneficial the increase in fat was not clearly so, and not even harmless, because of the possibility that it had passed through unutilized. No fat absorption experiments were carried out but it seems clear from the maintenance, let alone the gain, of weight, coincident with the sharp reduction in carbohydrate, that the fat must have been largely if not entirely utilized. These experiments indicate therefore not only that fat is much less harmful, than carbohydrate, if indeed fat per se is harmful at all, but they also additionally indicate that the carbohydrates themselves are a cause of arthritis especially since the third element of diet, protein, was actually increased in one case.[14]

In only certain selected cases where the disease is not hopelessly chronic and the age and condition of the patient are such that lessened activity of the arthritis can be clearly appreciated, can such experiments be carried out. Furthermore gastric and intestinal digestion must be quite equal to the digestion of fat in such large quantities as are necessitated in this "experimentum crucis." Again, the reduction of carbohydrate required to influence the arthritis must be relatively moderate so that the caloric value removed may be replaced by that from fat. It is also essential that the probationary unrestricted diet shall properly reflect the nutritive equilibrium of the subject and itself be not too high in caloric value for this level to be approximated later by the addition of fat.

[14] Two other experiments in which the protein was increased by a considerable margin have since apparently further indicated this. It will be noted that there is here some evidence that a relatively minor role for evil is played by protein.

The use of fat in such large quantities is not necessarily a clinical desideratum, even when the experiment can be carried out, and was for experiment only. For the reasons above given the evidence from the series reported, although suggestive, was not conclusive as to the possibility of what could be accomplished under favorable circumstances until the last experiments. Even in the less satisfactory types, however, such as the first nine of the series here quoted it is fairly clear that fat can be used with more or less satisfaction to the nutritive necessities. The difficulty of obtaining circumstances favorable to experimentation determines the reporting of these cases now. In advanced cases such experiments are often not clear cut and it seems possible that factors other than those originally causing the arthritis enter into the problem. It would then appear necessary not only to cut off largely the supply of toxin which caused the arthritis but additionally to influence various tissue cells, particularly perhaps in the muscles, to "utilization" of these products. Thus it appears from the study of a number of cases that a diet which is beneficial at the start in a severe case and is accompanied by a loss of weight may, after a time, operate less favorably and that a still lower diet and a further loss of weight secondary to it are required before improvement is again apparent.

In these instances it is conceivable that conditions within the tissue cells, the muscles for example, may then approximate the condition of so-called "basal metabolism" or even conditions of starvation. Under such circumstances the products of normal or pathological metabolism which reach them may be better handled or removed. This has been an hypothesis in the treatment of diabetes which recently has had confirmation. The corollary to this principle possibly explains the beneficial action, within limits, of radium, arsenic, thyroid extract and *x*-ray, the tissue cells in these instances being "whipped up" to some sort of heightened metabolism or activity by these agents. Only in the event that such heightened cellular activity could keep pace with the access of fresh toxin would these agents prove of value on this hypothesis.

There can be no question furthermore from clinical grounds alone that in certain borderland cases exercise importantly influences the "rheumatic" symptoms and it is conceivable that the modus operandi here is much the same and depends upon the "utilization" of intracellular substances.

The use of diet as advocated in this condition is not indefinite as directed toward thinning the fat individuals and fattening the thin, but specifically to reduce a source of toxin. The possibility remains that in some unknown way reduction in diet may modify the flora of the intestine and that this modification may result in changes in their elaborations. There may be a reduced quantity of bacterial split products of carbohydrate and protein. Again the benefits of a reduced diet may be referable to the actual metabolism of the

tissue cells themselves and the lessened demand upon them. There is strong ground for believing that whatever the mechanism within the intestinal tract this last factor also plays a definite role. Whether or no the mechanism concerned be in fact that of bacterial activity within the intestine the method described affords a means of controlling the pathological process secondary to it.

Among attempts made to determine whether bacterial activity is a factor here was the administration of capsules of trimethol a substance[15] which is alleged to inhibit bacterial activity without interference with digestion or any toxic results from the substance itself. This was given a trial in Cases XXXVIII and XLIII but with no benefit.

Certain other points deserve mention. It is interesting to note that bone changes may apparently precede the clinical symptoms of arthritis. Not infrequently the *x*-ray will show changes, along the shafts of the bones, which give no clinical symptoms and have existed presumably longer than the joint trouble of which the patient complains. In some instances showing acute involvement of the finger-joints of only one, three or four weeks' duration (Case XXXIII) *x*-ray of the phalanges may show these overgrowths and rarification which would seem to be of longer standing. Furthermore in certain cases the subject of headache, neurasthenia and other conditions not apparently related to arthritis and having no clear etiology, *x*-ray may show the same changes. In the absence of a history of arthritis or "rheumatism" this can sometimes be regarded as a symptom of an underlying disturbance having something in common with arthritis.

Some such cases treated along parallel lines have borne this out in their clinical response, and it is suggested that in such doubtful cases the *x*-ray may yield important evidence as to the nature of the underlying trouble. Again in certain cases where there is doubt as to the exact nature of an arthritis, in the knee for example; when there are no other joints involved and the process seems local; *x*-ray of the hands may show a striking and surprising degree of involvement which at once proves the arthritic process to be widespread and systemic. In such doubtful cases it is well to include routinely *x*-ray of the hands.

It is something of an argument for the identity of the several types of arthritis, atrophic, hypertrophic and mixed, that they may all respond to diet including the fibrous nodules. These last may disappear entirely. The type of arthritis which seems to respond less well or sometimes not at all to these dietary procedures is the so-called dry type[16] of primary progressive polyarthritis, involving the tendons rather than the other periarticular structures.

[15] Thomas Leaming & Co., New York.

[16] Lewellyn F. Barker: The Clinical Diagnosis of Internal Diseases, Monographic Medicine, iv, 93 *et seq.* D. Appleton & Co., New York and London.

It is noteworthy that some cases of long standing involving clinically nothing more than the terminal phalangeal joints of the hand respond with as much difficulty as though more important joints were concerned and the whole health of the individual reduced in consequence. In other words the limited extent of an arthritis does not necessarily imply facility of treatment and conversely a widespread involvement may subside surprisingly easily.

It should be borne in mind in considering responses of only moderate degree that they occur for the most part in patients the subject of chronic arthritis, generally of poor nutrition, and in the later decades of life. It is of course precisely the most advanced and difficult cases which are most ready to take up treatment and exceptionally is there opportunity to treat arthritis unaccompanied by sequelæ.[17] It is important again to emphasize the necessity of caution in carrying out treatment along these lines, as elsewhere discussed in detail.

Conclusions. 1. Experiments are cited in which it has been possible to relieve patients of all or practically all, symptoms of diffuse arthritis by a large curtailment of carbohydrate coincidently with the ingestion of fat in such increased amounts as to make up or exceed this caloric deficit. When the protein intake has been kept approximately constant some such patients have actually gained weight while convalescing. This evidence by exclusion ascribes an injurious role to carbohydrate, is additional to that already published and is corroboratory of it.

2. It is difficult to avoid the conclusion that fat, while it cannot be used with impunity in treating these cases, plays a relatively harmless role in marked contrast to carbohydrate. It can apparently be used in many cases to meet, more or less, the loss of weight which would otherwise ensue and in certain selected cases to meet it entirely or even to cause the patient to gain weight.

3. The difference in the effects of large amounts of carbohydrate when ingested by normal individuals and by subjects of rheumatoid arthritis is not reflected in the carbon dioxide tension of the alveolar air under the limited conditions of the experiments.

[17] The exact proportion of cases in which clinical benefit may be expected, cannot be given, but is indicated in general with some of the determining factors in the third paper, loc. cit.

# THE SYMTOMATOLOGY AND TREATMENT OF ARTERIOSCLEROSIS.[1]

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It is not my purpose to go into the more complicated scientific aspects of cardiovascular disease, but to give a practical analysis of the problem as determined by the essayist's experience and the experience of men in practice. The writings on the subject are voluminous and the unsolved truths are legion. The facts known about what the disease is in its development, its causes, and its manifestations, are far outweighed by speculative theories; so that even though the condition has long been recognized, our knowledge of its intricate processes is as yet in the field of experimentation and discovery.

Galen was the first to refer to the character of vessels, their softness and hardness, but not until comparatively modern times have we had an appreciation of arterial disease. Morgagni was the first to throw any light on the subject and the discovery of the circulation by Harvey led to a consideration of blood-pressure. Blood-pressure was first estimated by Hales, in 1727, in glass tubes, and the mercury column was not brought into use until about one hundred years later. The term arteriosclerosis was adopted by Lobstein in Paris in 1833, and it was von Basch, of Vienna, who by animal experimentation and clinical observation laid the foundation of our present-day knowledge of the problem of arteriosclerosis. In 1879 Mahomed, of Guy's Hospital, London, recognized the importance of rising blood-pressure and introduced the term pre-albuminuric stage of Bright's disease, which corresponds with the presclerosis type and the hyperpietic type of modern authors. Virchow, in his *Archives*, was the first to place arteriosclerosis on its modern basis.

The problem of blood-pressure is not well understood, and today we are unable to say just what a normal blood-pressure is. However, there are many facts that we do know. We know that pressure rises with advancing years, that at birth, systolic pressure is in approximate range of 35 to 55, and that a systolic pressure of over 150 at middle life is not normal. We know that systolic blood-pressure tends to rise with advancing years, but diastolic rise is not proportionate; hence an increase of amplitude or pulse-pressure. It is impossible to formulate a normal curve of daily life, for so many mental and physical factors enter in that we

[1] Read by invitation before the Northern Tri-State Medical Association, Toledo, Ohio, January 10, 1916, and Twelfth Councillar District of Indiana, Fort Wayne, Ind., April 12, 1917.

cannot weigh accurately; so, at best, blood-pressure determinations can only be approximate. We know that we can have markedly sclerosed vessels with low blood-pressure and very high blood-pressure without evident sclerosis, so that pressure elevation does not necessarily depend upon sclerosis. Even though blood-pressure be only an approximate determination we have come to value the instruments of precision in its determination so that the auscultatory method of determination of both systolic and diastolic pressure has become a routine in practice. The normal diastolic pressure under middle life is approximated at 80 or 90 to a systolic of 125, and if over 90 is considered abnormal; then the ratio is diastolic to systolic as 3 to 4 and the pulse pressure to systolic as 1 to 4. The factors bearing on blood-pressure, both static and dynamic, are so complex, such as the volume of wave, the pressure, the tone and density of walls, the big pulse with low pressure and the thready pulse with high pressure, the effect of meals, the time of day, the temperament or training of the individual, the viscosity of blood, lung capacity, the hormones, etc., that certain able experimenters doubt the value of all or any scientific gauge of blood-pressure, and if such be true, our finer distinctions or deductions made from changes in pressure must be more or less speculative.

The modern tendency is not to regard arteriosclerosis as a disease but as an anatomical result of various pathological processes. A clinical classification given by Allbutt and accepted by Osler is: (1) high pressure arteriosclerosis (hyperpiesia and chronic renal disease); (2) involutionary or decrescent (senile); (3) infectious or toxic (typhoid, syphilis, diabetes, lead). Hyperpiesia (Huchard's presclerosis, von Basch's latent sclerosis) goes over a period of forty to sixty years of age with an average duration of ten to twenty years, and this is the type that brings death by cerebral hemorrhage or cardiac defeat. The decrescent form or senile form of arteriosclerosis begins at fifty or sixty and exists over an indefinite period. In either form chronic renal disease may be present, but not necessarily so. Observation has shown that arteriosclerosis may uncommonly occur in early life. Von Romberg observed a case at the age of twelve years. Autopsy work in asylums has shown degrees of sclerosis not to be uncommon in young people. However, its character is fibrous rather than atheromatous. These cases are considered infectious in cause, and syphilis plays no small part aside from the acute infections and tuberculosis. The causes of arteriosclerosis are not within the scope of this paper, and I shall take up a consideration of the symptomatology. Adami says arteriorenal problems are the most complicated and obscure in the whole of pathology, and if this be true of pathology it must be equally true of etiology and symptomatology.

Just what part the kidney plays in cardiovascular disease is not

known, for our observations have been incomplete—autopsy findings have come too much in the terminal stages when the processes have been made obscure. In discussion of symptoms we will keep in mind the simple classification into two types, viz., the hyperpietic and the involutionary or decrescent form. The hyperpietic form may occur, in fact more often does occur, independent of primary renal involvement, and is the type of case that the German school terms essential hypertension. However, there is another group of cases under this type of hypertension without evident sclerosis that is secondary to renal involvement, and this group the Germans term nephritic hypertension. Osler as far back as 1898 referred to this classification. Prof. Krehl, of Heidelberg, whose authority in these problems is beyond question, says we tend to attribute all cases of high blood-pressure to nephritis, which is untrue. Stengel says that albuminuria in arteriosclerosis is not necessarily evidence of Bright's disease. Tyson and Janeway are of the same opinion. Kidney function tests, careful clinical observation in conjunction with pathological investigation, promises to give us a more definite understanding of this problem. In the decrescent form of arteriosclerosis the form that shows the sclerosed and atheromatous arteries with low blood-pressure frequently, the kidney process is the arteriosclerotic type more often and is not necessarily a badly diseased kidney. Osler refers to traces of albumin in elderly persons, and asks how many persons over fifty have kidney histologically normal. The red granular kidney always gives a definite hypertension in contradistinction to the arteriosclerotic kidney, which is atrophic and is associated with low pressures. Mahomed was the first to recognize that certain cases of hypertension were not associated with renal disease, but considered them pre-albuminuric states. We now know that albuminuria in association with hypertension is not necessarily Bright's disease.

Janeway found in making observations on 130 cases with blood-pressures above 200 that 17 gave no evidence of renal involvement, and later he says autopsies tend to prove that hyperpietic kidneys give little or no evidence of change. It is the hyperpietic case that bears venesection well and is improved while the kidney involved case is not. Arteriosclerosis is a resultant of many diseases and conditions and does not in itself give any specific symptomatic series. It has no uniform symptoms of its own, unless we accept the hypothesis of Virchow, who considered it an inflammatory process—an arteritis. He regarded it as an inflammatory disease of the arteries having a definite course with which was associated a slight temperature rise. Allbutt regards the symptoms of arteriosclerosis a tangled skein, some of which have been combed aleady into order and others remain confused. Von Basch considered hypertension to be caused by sclerosis, and when not recognized

in palpable vessels thought it to be regional, such as splanchnic. The same opinion was held by Huchard, who maintained that presclerosis was immediate on sclerosis. The hyperpietic case may be without symptoms other than hypertension. When dyspnea and sternocardia are evident the case is no longer early. There is no question but that a hyperpietic case can be detected when it is curable. The common subjective symptoms in association with hyperpiesia are substernal distress on exertion, transitory hitches in speech, vertigo, numbness of extremities, sometimes transitory paresis of hand or arm, tendency to tire, mental depression, insomnia, headache, irritability, and often signs of nervous dyspepsia. If asked to describe his symptoms the patient's story is often vague; he is cognizant of ailing but scarcely knows how, and feels the need of stimulation. It is this type of case that is often loosely diagnosed neurasthenia. The pulse-rate may or may not be increased but has a suggestion of hypertension and extrasystoles are often present.

The heart shows a degree of hypertrophy, more particular of the left ventricle, with accentuated aortic second sound. Later, hypertrophy gives way to dilatation and mitral insufficiency is made evident. The palpable arteries will have become thickened and tortuous. The large veins on hands show distention, and slight edema may be found on the anterior tibial surfaces. The urine may show traces of albumin without formed elements. The aorta is often dilated and the second sound becomes much clearer as it approaches the surface of the thorax. The elongation of the aorta permits falling of the heart base, so it assumes a more horizontal position, which throws the apex out. When atheroma is present the second sound may become more metallic. An accentuation of the aortic second must be differentiated from nervousness, and when normally the vessel is near the chest wall. Pulsus alternans is occasionally observed. These arrhythmias are supposed to be caused by increased irritability of the heart muscle under strain of hypertension, and are relieved by reduction of pressure. Galloping rhythm is occasionally present. In some cases the aorta may be palpated in the episternal notch. The two radial pulses may show differences which suggests invasion of the subclavian by the atheromatous process. It is impossible to differentiate the syphilitic type of aortitis from the arteriosclerotic in behavior, but pathologically the syphilitic more often invades the ascending portion of the arch. A widened aortic area on percussion is very commonly made out. Attacks of dyspnea are very common and are rather instantaneously relieved with nitroglycerin; the same is true of anginoid pains. However, some authorities take exception to calling them anginoid and use the term cardiac pain. A large percentage of these cases show tenderness on percussion over the precordium. In the paroxysmal dyspnea of high

pressures, pulmonary edema is often associated. Emphysema is more commonly associated with the decrescent type of arteriosclerosis. Bronchitis is more common in the hyperpietic type. Migraine is not uncommonly a forerunner of the hypertension type, but in the associated head pains, cerebral syphilis must always be considered. The vertigo of arteriosclerosis is supposed to be aural in type. Epileptoid seizures are not uncommon in arteriosclerosis, especially the hyperpietic type, but here one must differentiate a degree of uremia with brain edema. Cerebral hemorrhage is the most serious aspect of hyperpiesia, for it often occurs before subjective symptoms and before vascular change is evident. The only warning may be transitory numbness or slight mental confusion. These transitory phases may well be called intermittent claudication or angiospasm, and are more often associated with the hyperpietic type while aphasia is probably with the decrescent type. One not infrequently observes rather profound apoplectic seizures that regain consciousness and improve decidedly. No doubt this type case sustained a local brain edema or spasm of cerebral vessel (but this is questioned by certain authorities) or punctate hemorrhages that are not extensive. Molecular fatigue has been advanced as a probable cause of such attacks. Osler regards these attacks of paresis, which are transitory, as resultant of vessel spasm, on the grounds that sclerosis encourages spasm. Russell holds the same opinion. Allbutt disputes this theory and says that the sclerosed vessel is less subject to vasomotor change than the normal vessel, and if such a cause were true we would have such phases frequent in normal individuals, and says that death in coma is due to increased intracranial pressure, which is not increased by constriction of a vessel. Cases autopsied where these transitory phases were historical and where death was caused by apoplexy show numerous old punctate hemorrhages.

Forbes Robertson says that after months or years minute hemorrhages may be represented only by tiny sclerotic patches, and in brains of the insane such islets are often seen. The French have observed in doing repeated lumbar punctures in cases of high blood-pressure, the fluid is often bloody and shows signs of old hemorrhage, but 20 to 25 c.c. must be taken out to discover blood cells or hemoglobin. Other observers think these hemorrhages are due to hemolytic toxins, but this occurs in the nephritic type. The advisability of bleeding in an individual case of apoplexy is difficult to determine, and it is often remarked that it either kills or cures. The symptoms of the decrescent or involutionary type of sclerosis may be *nil*, and this condition may not be incompatible with long years. Emaciation is generally evident and may be cachectic in character. When palsies occur they are atrophic and not hemorrhagic. This type of case is very commonly found in our asylums. The kidney is fibrosed and is a part of the general

degenerative process. Softening of the brain occurs in this type, and such an arteriosclerotic may exist for years, so that the old saying that a man is as old as his arteries is not quite true. Hemorrhage is not common, but infarct emboli and thrombosis may occur. A large percentage of these cases show eye-ground changes. Such a patient's mental state is different from the hyperpietic's in the fact that he becomes more or less passive while the hyperpietic is given to spells of depression. The heart of the decrescent type is atrophic, in contradistinction the hypertrophic heart of the hyperpietic type and the decrescent type rarely meets the cardiac defeat which is common in the hyperpietic. Arteriosclerosis advanced has no treatment, but the state of high blood-pressure which may be regarded presclerotic has. While it is not within the scope of this paper to consider causes, we cannot rationally discuss treatment without briefly considering etiology at least in a speculative way. The rise of blood-pressure in the hyperpietic must be due to increased peripheral resistance, and this must result from narrowing of the peripheral arterial tree or increased viscosity of blood, or both. The constriction may be due to disordered metabolism or intoxication, which may act directly on the vasomotor centre or upon the vessels themselves. Hyperpietic states are amenable to treatment if taken early. Hence, our problem is to determine the degree or time of existence. The early case when put at rest in bed, with encouragement of elimination, for a period of time, if favorable, will show a definite lowering of pressure, a lessened accentuation of the aortic second and a lessening of cardiac hypertrophy. I am sure it is the experience of everyone who has observed these cardiovascular cases to not uncommonly find a return to apparently normal after an unfavorable prognosis had been given. If this supposed early case does not respond to such management then we must conclude that the vascular system has sustained stresses that are not amenable to management and therefore the prognosis becomes less favorable. These patients must not be treated at the expense of their well-being. It requires extreme tact in rightly managing them, for there is a tendency to live around the blood-pressure and become very introspective. Immediately they regard themselves as candidates for apoplexy. They very quickly label themselves as high blood-pressure victims and become intensely neurotic. The blood-pressure estimations must always be favorable to their improvement. Here truly can we say that blood-pressure is a very changeable thing; that its determination can never be made definite; that our means of estimating are only approximate at best; that blood-pressure is a minor thing; that the condition as a whole is our chief concern. It is our duty to take the patient from all strenuousness of life and discipline him in a régime which is favorable to improvement, for after all the problem is one of man-

agement rather than a particular drug. We must restrict the diet, particularly in respect to meats, condiments, stimulants, sugars, and fats. If obese, the cardiovascular mechanism will be relieved by reduction in weight. Many patients are greatly improved in subjective symptoms, such as dyspnea, cardiac pain, and fatigue on reduction of weight, which gives a corresponding and often disproportionate reduction in blood-pressure. In severe cases with obesity reduction may best be managed by rest in bed over a period of months. Overeating, directly or indirectly, is a factor of no small importance in producing cardiovascular disease, be it due to putrefactive substances from the bowel or overtaxing of excretory organs by unused food material. I shall not enter into a detailed discussion on a dietary, as certain principles in feeding are to be observed with which we are generally acquainted, and the problem is more or less an individual one. Just how much or how little salt may be given in an individual case is often speculation. However, we do know that withholding salt in cases with edema or pre-edemic states gives encouraging results. Careful dietary, management, and well-regulated exercise will do much in the early cases of hyperpiesia, and no kind of exercise is better than walking. In the more advanced cases a period of rest in bed is essential, with warmth, passive exercises, and baths. A mild and equable climate with moderate elevation is desirable. Excessively hot baths are generally not beneficial and do not give substantial relief, and may give the patient discomfort. The desirable bath seems to be neutral at about 33° or 34° C., and gradually brought to 40°. Nearly all baths affect the cardiac mechanism and should be given cautiously. The advantages of treatment aside from careful regulation of diet, encouragement of elimination, and gradation of activity are probably overestimated. Authors disagree on value of warm or hot baths, but the tendency is to get away from the hot bath. The quantity of water taken depends upon the individual case; but speaking generally the liquid intake of the hyperpietic case should be restricted to $1\frac{1}{2}$ or 2 liters daily. The radium bath (natural water) has become popular in the management of these cases. It is claimed that it lessens viscosity of blood, increases diuresis, and encourages uric-acid elimination, and hence lowers blood-pressure. Electric-light baths have been advised but should be used in the same careful way as tub baths, starting at lower temperature and gradually increasing to 90° or 100° F. Electricity in the way of high-frequency currents is advised by some and discouraged by others. I believe the consensus of opinion is that it lowers peripheral resistance and, of course, lowers pressure. Venesection is of value in the high-tensioned case, is of value in warding off a crisis, and may be repeated at intervals in certain selected cases. It is a very simple procedure by placing a towel as a tourniquet above the elbow, tapping the space at the bend

degenerative process. Softening of the brain occurs in this type, and such an arteriosclerotic may exist for years, so that the old saying that a man is as old as his arteries is not quite true. Hemorrhage is not common, but infarct emboli and thrombosis may occur. A large percentage of these cases show eye-ground changes. Such a patient's mental state is different from the hyperpietic's in the fact that he becomes more or less passive while the hyperpietic is given to spells of depression. The heart of the decrescent type is atrophic, in contradistinction the hypertrophic heart of the hyperpietic type and the decrescent type rarely meets the cardiac defeat which is common in the hyperpietic. Arteriosclerosis advanced has no treatment, but the state of high blood-pressure which may be regarded presclerotic has. While it is not within the scope of this paper to consider causes, we cannot rationally discuss treatment without briefly considering etiology at least in a speculative way. The rise of blood-pressure in the hyperpietic must be due to increased peripheral resistance, and this must result from narrowing of the peripheral arterial tree or increased viscosity of blood, or both. The constriction may be due to disordered metabolism or intoxication, which may act directly on the vasomotor centre or upon the vessels themselves. Hyperpietic states are amenable to treatment if taken early. Hence, our problem is to determine the degree or time of existence. The early case when put at rest in bed, with encouragement of elimination, for a period of time, if favorable, will show a definite lowering of pressure, a lessened accentuation of the aortic second and a lessening of cardiac hypertrophy. I am sure it is the experience of everyone who has observed these cardiovascular cases to not uncommonly find a return to apparently normal after an unfavorable prognosis had been given. If this supposed early case does not respond to such management then we must conclude that the vascular system has sustained stresses that are not amenable to management and therefore the prognosis becomes less favorable. These patients must not be treated at the expense of their well-being. It requires extreme tact in rightly managing them, for there is a tendency to live around the blood-pressure and become very introspective. Immediately they regard themselves as candidates for apoplexy. They very quickly label themselves as high blood-pressure victims and become intensely neurotic. The blood-pressure estimations must always be favorable to their improvement. Here truly can we say that blood-pressure is a very changeable thing; that its determination can never be made definite; that our means of estimating are only approximate at best; that blood-pressure is a minor thing; that the condition as a whole is our chief concern. It is our duty to take the patient from all strenuousness of life and discipline him in a régime which is favorable to improvement, for after all the problem is one of man-

agement rather than a particular drug. We must restrict the diet, particularly in respect to meats, condiments, stimulants, sugars, and fats. If obese, the cardiovascular mechanism will be relieved by reduction in weight. Many patients are greatly improved in subjective symptoms, such as dyspnea, cardiac pain, and fatigue on reduction of weight, which gives a corresponding and often disproportionate reduction in blood-pressure. In severe cases with obesity reduction may best be managed by rest in bed over a period of months. Overeating, directly or indirectly, is a factor of no small importance in producing cardiovascular disease, be it due to putrefactive substances from the bowel or overtaxing of excretory organs by unused food material. I shall not enter into a detailed discussion on a dietary, as certain principles in feeding are to be observed with which we are generally acquainted, and the problem is more or less an individual one. Just how much or how little salt may be given in an individual case is often speculation. However, we do know that withholding salt in cases with edema or pre-edemic states gives encouraging results. Careful dietary, management, and well-regulated exercise will do much in the early cases of hyperpiesia, and no kind of exercise is better than walking. In the more advanced cases a period of rest in bed is essential, with warmth, passive exercises, and baths. A mild and equable climate with moderate elevation is desirable. Excessively hot baths are generally not beneficial and do not give substantial relief, and may give the patient discomfort. The desirable bath seems to be neutral at about 33° or 34° C., and gradually brought to 40°. Nearly all baths affect the cardiac mechanism and should be given cautiously. The advantages of treatment aside from careful regulation of diet, encouragement of elimination, and gradation of activity are probably overestimated. Authors disagree on value of warm or hot baths, but the tendency is to get away from the hot bath. The quantity of water taken depends upon the individual case; but speaking generally the liquid intake of the hyperpietic case should be restricted to $1\frac{1}{2}$ or 2 liters daily. The radium bath (natural water) has become popular in the management of these cases. It is claimed that it lessens viscosity of blood, increases diuresis, and encourages uric-acid elimination, and hence lowers blood-pressure. Electric-light baths have been advised but should be used in the same careful way as tub baths, starting at lower temperature and gradually increasing to 90° or 100° F. Electricity in the way of high-frequency currents is advised by some and discouraged by others. I believe the consensus of opinion is that it lowers peripheral resistance and, of course, lowers pressure. Venesection is of value in the high-tensioned case, is of value in warding off a crisis, and may be repeated at intervals in certain selected cases. It is a very simple procedure by placing a towel as a tourniquet above the elbow, tapping the space at the bend

of the elbow to bring out the vein, scrubbing with alcohol, and inserting a needle of sufficient lumen to permit a free flow, which is encouraged by having the patient alternately close and open his hand. Bleeding is contra-indicated in cases of high pressure, with kidney involvement when there is a degree of anemia. The blood-pressure is lowered for only a short period, but a sense of relief is experienced from their pressure symptoms. It is contra-indicated in the decrescent form with low blood-pressure. In treating blood-pressure we must appreciate that the process is largely compensatory, and our interference should be cautious. Therefore, insofar as vasodilator drugs fail to relieve a cause as a toxin we must consider how much lowering of pressure in this way brings about good. However, if our experience teaches us that symptoms can be relieved and the patient be given no hazards, symptomatic treatment is justifiable, and so long as we are unable to prove that their high pressures may be due in part at least to toxin irritating the vasomotor centre, it seems quite rational to give vasodilatators, such as nitrites, even over an extended period of time if pressures are lowered and the patient is made more comfortable without untoward signs, such as edema or a failing myocardium. Nitroglycerin in drop doses has a definite place in relieving cardiac or anginoid pains, and I not infrequently place it in a patient's hands to be used cautiously when indicated. Just how so-called vasodilatators act is speculation. It is accepted that diastolic pressure is lowered, and the question is whether by peripheral dilatation or splanchnic dilatation or by lowering cardiac energy. We should watch not only our systolic but diastolic pressure when administering such drugs. At best, drug therapy is only an adjunct to the treatment of these cases. Mercury is employed, but in the non-syphilitic case I have had no experience. Iodids unquestionably have value if given intensively over a period of time with alkalies even though animal experimentation is to the contrary, but we cannot compare normal with abnormal arteries. Just how is speculation, whether by lessening viscosity of the blood, by lessening spasm, or by excitement of the thyroid. The iodids may be given in combination with bromids. For a failing heart no drug is superior to strychnin. Diuretin is used in cases of anginoid pains, but I have seen no benefit from its administration. I have no experience with the antisclerotic serums, and the general impression is that they are useless. Aspirin and sodium salicylate lower pressure and have some value. Vasotonin, which is a combination of yohimbin and urethane, has not proved useful. Fibrolysin as having value is a question. Thyroid extract seems to be of little or no value. When unable to relieve peripheral resistance against a failing heart, digitalis is indicated. A good index is to administer digitalis when the diastolic pressure is rising and pulse-pressure lessening. Strophanthin or strophanthon may be employed, but

at times are toxic. The principle to be adhered to in the treatment of arteriosclerosis is not the sclerosis but the morbid changes, be they toxic or otherwise. In the senile type we have nothing to treat because it is as natural as gray hair or arcus senilis. On general principles tonic treatment is indicated, and if hyperpiesia should develop, they should be managed as the hyperpietic.

## FOCAL SEPSIS IN THE GENITO-URINARY TRACT AS A CAUSE OF CONSTITUTIONAL DISEASE.[1]

By B. A. Thomas, M.D.,

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The importance of focal sepsis in its relationship to the genito-urinary tract entitles it to a prominent position in the minds of internests, general surgeons, and the various specialists.

Among the numerous septic affections involving the genito-urinary system which, untreated, are prone to lead to constitutional involvement may be mentioned acute hematogenous suppurative nephritis, pyelitis, pyelonephritis, pyonephrosis with or without calculus, tuberculosis of the kidney, renal, and perirenal abscess, ureteritis, cystitis, especially the purulent type, prostatitis, seminal vesiculitis, epididymitis, orchitis, and urethritis.

I have observed patients who have spent large sums for the correction of pyorrhea alveolaris and other dental disorders, when the real cause of complaint was centered in chronically diseased seminal vesicles. I have heard of a case on whom hundreds of dollars were spent for extensive crown and bridge work, when seminal vesicle medication and massage, or vesiculotomy or vesiculectomy, would undoubtedly have sufficed to eradicate the constitutional affection from which the patient suffered. I have treated patients, previously subjected to tonsillectomies unattended with benefit, so far as the chief indication for their performance was concerned, and observed immediate improvement when measures were directed to the diseased seminal vesicles. I have seen patients complaining of rheumatism, investigated by elaborate metabolic studies and placed on restricted diet lists, when vasopuncture and spermatocystic medication, or drainage of a seminal pyovesiculosis, would doubtless have effected a cure. How many patients treated by the general practitioner, or for that matter by the internest, the general surgeon, the orthopedist, the neurologist or the psychiatrist, in our best hospitals, complaining of symptoms

[1] Read by invitation before the Philadelphia County Medical Society, April 12, 1916, and received for publication June 11, 1916.

possibly referable to diseased urethral adnexa, ever receive an examination by rectal palpation, etc., or if so by any one really qualified to express an opinion? Assuredly, the average hospital resident, to mention the least, knows little or nothing, clinically, about inflammatory prostatic involvement, much less disease of the seminal vesicles. The above assertions are made in no spirit of vindictive criticism, but solely with the desire and hope that the profession generally may be awakened to a realization of the fact that chronic seminal vesiculitis is a far more prevalent disease than the average physician surmises, that it is not accorded the consideration its medical importance demands, and that it masquerades under a manifold symptomatology finding its expression ofttimes remote from the urinary tract. In view of the high percentage of the male population who have had gonorrhea, and realizing that 90 per cent. at least of these have had posterior urethral involvement, it must be apparent to everyone that, comparatively, there are few men who have not experienced a spermatocystitis.

The time has arrived for every practitioner of medicine to recall the anatomy of the spermatic tract—vesicle, ampulla of vas, and ejaculatory duct. Three facts stand out preëminently: (1) the tortuous nature of these tubular structures, presenting an extensive mucous surface fitted with ramifying diverticula, characterized by minute cellules and ridges, rendering the tract, when infected, the worst drained of any in the human body; (2) a most complex and delicate nervous mechanism, filaments from the hypogastric plexus penetrating intimately the muscular and mucous coats of these delicate spermatic tubular structures. Thus owing to the correlation of the prostatic, vesical, pelvic, sacral, lumbar, and hypogastric nerve plexuses the occurrence of pains referred to the anal, perineal, genital, hypogastric, and lumbar regions, also to the hip-joint, sacro-iliac synchrondroses, and the thighs, becomes readily explainable; (3) the gross anatomical relationship, rendering these structures, on account of a more or less inaccessible situation, difficult of treatment, either conservatively or radically.

It is almost incredible that the seminal vesicles so closely associated with the prostate should have escaped so long consideration in investigation of the pathology of deep urethral infection while the prostate has been so thoroughly studied. Indeed in text-books, universally, the vesicles have been alluded to casually or entirely neglected; yet I believe that they share in infection equally as often as the prostate, and are far more prevalent septic foci as causes for certain neurological and constitutional disorders.

Epididymitis is always associated with a spermatocystitis on the affected side, and recurrent epididymitis is invariably caused by a lingering infection of the seminal vesicle. The gleety discharge of a protracted gonorrheal infection is commonly due to a latent infec-

tion of the spermatic tract—the shreds originating in the vesicles—rather than a chronic process located in the prostate or posterior urethra.

As a pure gonorrheal cystitis is a condition that probably never occurs, so too are most infections of the seminal vesicles and prostate mixed. Indeed it is seldom that the gonococcus can be isolated from the vesicles either by massage or seminal vesiculotomy. On the contrary the vesicle is found to harbor a formidable array of pathogenic bacteria, among which may be named various strains of streptococci, pneumococci, staphylococci, coion bacilli, unknown Gram-negative diplococci, corynebacteria, and tubercle bacilli. Undoubtedly in many patients tagged with the diagnosis of "gonorrheal rheumatism," the gonococcus has ceased its onslaught and abandoned the trenches in the form of a chronic seminal vesiculitis, in favor of a mixed infection, of which one or more of the above-mentioned bacteria are the chief offenders. The time is ripe for the specialist as well as the general practitioner to appreciate the fact that bacterial foci, gonorrheal or non-specific, lurking often for years, in the spermatic vesicles are frequent causes for constitutional disorders in the guise of "rheumatism," articular and muscular, "rheumatoid arthritis," "arthritis deformans," "gout," hypertrophic arthritis, pains and peculiar sensations referred to the perineum, hips, thighs, back, and suprapubic regions, also a retinue of psychic disturbances as queer impulses, bordering on suicidal thoughts, panicky phobias, prone to occur on bridges, boats, trains, and in churches and theatres, dreadful dreams, loss of thought concentration, indifference to occupation and a perversion of moral character substantiating, on a pathological basis, certain tenets of the Freudian theory. To be more specific, I have frequently observed patients complaining of urinary difficulties due solely to a chronic periseminal vesiculitis and infiltration about the trigone and vesical neck, resulting in ureteral irritation and compression, and more particularly retention of urine, in one instance amounting to 15 ounces. The prevalence of epididymitis as a complication, more directly of seminal vesiculitis than of urethritis, has already been mentioned. Moreover, in this connection it should be mentioned that in the author's experience fully 50 per cent. of patients having passed through an epididymitis, exhibit a stricture of the vas deferens between the neck of the scrotum and the seminal vesicle, accounting in bilateral cases for a high percentage of sterility, not amenable to the operation of epididymovasostomy. Among other serious, if not constitutional, diseases which I have observed to be due to spermatocystitis are synovitis, arthritis, osteoperiosteitis, cystitis, pyelitis, pleurisy, endocarditis, general cutaneous eruptions, spermatorrhea, impotence, neurasthenia, and a plethora of nervous and mental conditions. Thus in comparison with diseased tonsils and pyorrhea

alveolaris, cryptic or septic infection of the seminal vesicles runs high, and I am not at all convinced that the greater evil does not rest with the vesicles. An abstract of a few case histories may be of interest:

CASE I.—P. H. B., aged forty years, had gonorrhea twenty years ago, followed by strictures, but claims he was all right until four years ago, when, after resumption of passage of sounds on himself, suffered an attack of urethral fever and urethral discharge lasting two or three weeks: Remissions of the discharge occurred and coincidently "rheumatism" of the hips and tremors of the thighs, associated with itching about the rectum for the past year. Patient is also troubled with some frequency of urination, and a few floating shreds are present in the urine. Sounds (Nos. 25 and 29 F.) passed easily through the posterior urethra. Rectal palpation revealed a palpable and tender right seminal vesicle, and the urine voided after massage showed an average of fourteen pus cells to the microscopic field.

Three months previously the patient had undergone a tonsillectomy, and recently an elaborate metabolic study and dietary precautions without material improvement. Under vesicular and prostatic massage with Janet irrigations and bacterin therapy, the pus cells in four weeks were reduced to five or six to the microscopic field and the tremors of the thighs had disappeared. Treatment was kept up for a few months and the patient discharged for the summer. Seen one year after his first visit he stated that, aside from a slight attack of "rheumatism" about six weeks after undertaking treatment, he had been free of attacks, with one exception, that occurring during the summer while in California.

CASE II.—A. C., aged twenty-eight years, contracted gonorrhea years ago, the attack lasting eight months; second attack four years ago, complicated by a bilateral epididymitis. His chief complaints were pain in the back, described by an orthopedist as relaxed sacro-iliac joints, premature ejaculations, and pain in left testicle, for which a well-known general surgeon had performed a varicocelectomy unattended by any relief. The general practitioner referring the case had prescribed nerve sedatives and given hygienic instructions. On examination per rectum the regions of both seminal vesicles were infiltrated and presented finely nodular or irregular areas. Both regions were abnormally tender and the prostate seemed to be uninvolved. Both epididymes were enlarged and nodular. The urine showed shreds and many clumps of pus cells after spermatocystic massage. The gonococcus serological test resulted weakly positive. Treatment consisted in periodic massage, irrigations, urethral dilatation and bacterin therapy. In less than a month, in patient's own words, he felt "very much better," and in less than two months he was discharged, apparently cured.

CASE III.—W. A., Jr., aged thirty years, in the course of a posterior gonorrheal urethritis, on the twentieth day of his illness, developed cystitis and a left-sided spermatocystitis and epididymitis: on the twenty-sixth day pleurisy, and on the twenty-eighth day a ureteropyelitis of the corresponding side. On the same day the patient received 4 c.c. of antigonococcic serum. Next day the urine was much clearer and the following day the patient felt much better, although pleuritic friction rub was still audible. Three days after the first injection he received a second dose of antitoxin. Two days later temperature, pulse, and respiration were normal and all signs of the more serious complications had disappeared. Eighteen days later local urethral treatment in the form of massage and irrigations could be resumed and eighteen days subsequently not a shred or pus cell could be found in the morning urine.

CASE IV.—C. J., aged twenty-eight years, came to the hospital, complaining of impotence. History elicited the facts that he had passed through three attacks of gonorrhea, once complicated with bubo. He had marked frequency of urination, rising six or eight times at night. The patient called attention to vague pains, loss of weight and vigor, disability from work, and nervousness to the point of tremors. Per rectum, both seminal vesicles were palpable and doughy and the prostate slightly boggy, especially on the right side, where it was subsequently discovered that he had a stricture of the vas deferens. The gonococcus serological test was weakly positive and the Wassermann negative. Vasopuncture for medication of the seminal vesicles, followed by sounds, irrigations, and a tonic for six months restored his pus tubes apparently to a normal condition, and at least rendered him potent sexually.

CASE V.—F. R., aged forty years, contracted gonorrhea for the first time sixteen years previously; was reinfected four years later, developed a prostatic abscess six years thereafter, and has had repeated attacks of epididymitis on both sides. One year ago the patient developed heart trouble and at present is practically bedridden with a recurrent attack of epididymitis of ten days' duration. On examination the right epididymis was found enlarged and subacutely tender; the left nodular but not tender. Per rectum the prostate and seminal vesicles on both sides were a mass of chronically inflamed and tender tissue. The urine was cloudy and full of shreds and pus. The heart was markedly dilated and associated with valvular disease and insufficiency. Blood-pressure averaged 230 (systolic). Wassermann was negative, but gonococcus serological test resulted medium positive. Treatment consisted, on the subsidence of the epididymitis, of massage and Janet irrigations, supplemented with an alternation of gonococcic and autogenous bacterins. For a time the patient showed some improvement, and he has been reported (a year later) to be still alive.

CASE VI.—J. McC., aged thirty-five years, acknowledged gonorrhea seven years before. At the time of his visit to the hospital he complained of pain in the left ankle and heel, also the right foot. Examination revealed a chronic prostatitis and a palpable and tender left seminal vesicle. Urine showed few shreds, but massage and microscopic examination of the subsequently voided urine demonstrated twenty pus cells to the one-sixth objective field. Wassermann and gonococcus serological tests were negative. Under massage, irrigations, and bacterin therapy in less than two weeks the left foot showed improvement and he was much better generally. This patient has been under treatment less than two months, and although he is not yet well, he is greatly improved in every respect. The prostate and vesicles appear normal on palpation and the urine is perfectly clear.

CASE VII.—A. L., aged fifty-five years, father of two healthy children. His chief complaints are dragging pains in both groins, lack of vigor physically and mentally, dark rings under eyes without cause, and a urethral discharge. Admitted having had gonorrhea thirty-five years ago and was treated four or five weeks. Patient stated that discharge appeared three months ago, associated with severe sharp pains in rectum; dragging pains in groins occurred only two weeks ago. He has no frequency of urination, but decided urgency. On rectal palpation, the prostate was not found to be enlarged, but considerable infiltration and induration of tissues in region of seminal vesicles and neck of bladder were demonstrable; moreover, microscopic examination of the urine after massage showed an average of twelve pus cells and many clumps of pus to the one-sixth objective field. Urethral examination revealed a chronic posterior urethritis and 15 ounces of residual urine. The Wassermann was negative, but the gonococcus serological test was weakly positive. This case is obviously one of retention of urine due to urinary obstruction on account of a seminal perivesiculitis and pericystitis. The usual treatment directed to the seminal vesicles and posterior urethra has already resulted in considerable improvement, although the case was seen only ten days ago.

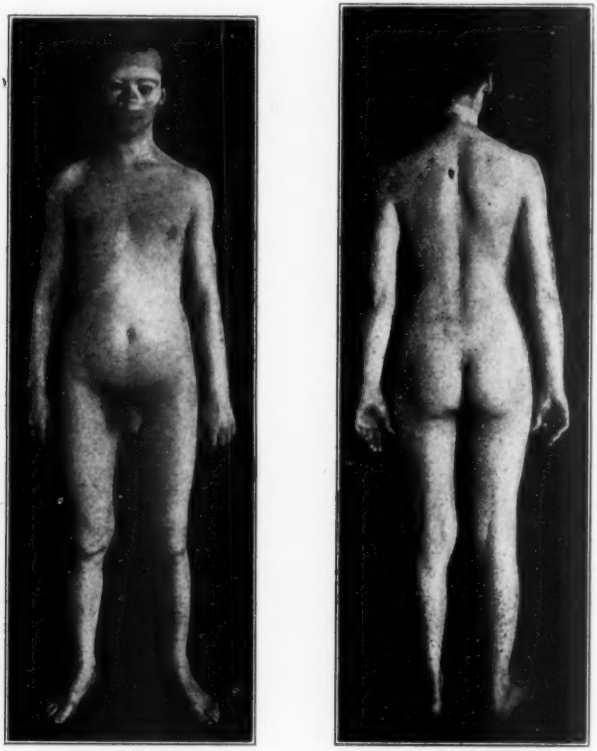
CASE VIII.—H. S., aged twenty-seven years, admitted gonorrhea for the first time five years ago, with two recurrences since, the present attack being of two months' duration. A slight mucopurulent discharge was present at the external urinary meatus. The urine was full of shreds and rectal examination demonstrated a prostate normal by palpation, although subsequently a stricture of large size was found in the posterior urethra. Although the patient received no drug other than salol, ten days after his first visit, he called my attention to a punctate, papular eruption on the arms, which in the course of two weeks developed into a general papulosquamous roseola, which after negative Wassermann and positive gonococcus serological tests was diagnosed as a *gonorrheal*

*roseola* (Fig. 1). This opinion was concurred in by Dr. Jay F. Schamberg. The administration of antigonococcic serum on three occasions in the course of eight days, possessed an immediate and specific effect and the eruption had completely disappeared by the end of two weeks. At this time also the gonococcus serological test became negative. Subsequent treatment for a few weeks was devoted to the stricture and chronic posterior urethritis.

FIG. 1.—H. S. Gonorrheal roseola of two weeks' duration. (Photograph of colored drawing.) See Case VIII.

CASE IX.—E. I. B., aged thirty-five years, was referred to me with a "rash all over the body," of three weeks' duration, with the history that he had three small chancres seven years previously, when he had his first attack of gonorrhea. He admitted four attacks of urethritis, the last two months ago or five weeks prior to the present cutaneous eruption. Temperature and pulse were normal. The epithrochlear lymph nodes were palpable, but the postcervical were not. The entire body, excepting face and palms, were covered with pin-point to 2 mm.-sized, punctate, bright red papules, each with definite infiltration (Fig. 2). The urine was cloudy and contained many heavy shreds. Per rectum the prostate

felt normal, but both seminal vesicles were enlarged, hard, and unduly sensitive. The Wassermann was negative, but the gonococcus serological test resulted weakly positive. No subsidence was noted in roseola for two weeks under the usual treatment, including gonococcic bacterin, when bilateral vasopuncture was performed and both seminal vesicles medicated with a 10 per cent. solution of collargol. Ten days later the eruption was scarcely



Front view. Back view.

FIG. 2.—E. I. B. Gonorrheal roseola of three weeks' duration. See Case IX.

visible. Although from this time on, the patient never exhibited a return of further constitutional trouble, in view of a persistent nodule in left vesicle and an excess of pus in his urine after massage, he has been advised to have a repetition of vasopuncture or seminal vesiculotomy or vesiculectomy.

The medical profession owes a debt of gratitude to Jordan Lloyd of Birmingham, England, for his pioneer work as far back as

1888 in directing attention to the importance of spermatocystitis, the significance of its pathology and symptomatology and the demonstration of an operative procedure of merit, also to Fuller and Belfield in this country, for popularizing the operative treatment of this obdurate disease.

It is undoubtedly true that the vast majority of patients who fall victims of gonorrhea, complicated by seminal vesiculitis and prostatis, sustain what is commonly known as the catarrhal form, and the inflammation, after running its usual course, ends in resolution. Again in those men suffering from a more deeply seated form of the disease, proper massage and total irrigations suffice in most cases to effect a satisfactory cure. Thus operation should be considered only after massage has failed and since the particular operative procedure to be adopted depends upon the morbid process present in the vesicle, vas or ejaculatory duct, it behooves the surgeon to ascertain the nature and extent of the pathological lesions present. This knowledge may be acquired by rectal palpation, massage, microscopic examination of the expressed vesicular content, bacteriological examination, needle puncture of the vas in an attempt to detect strictures by the injection of solutions of sterile water and methylene blue and occasionally by roentgenography of the vesicles. Dependent upon the information obtained, massage and irrigations with or without bacterin therapy, vasopuncture, and spermatocystitic medication, repeated if necessary, vesiculotomy and vesiculectomy must be done in indicated cases, if we hope to eradicate this intractable disease and avoid, in many cases, systemic invasion.

## HEAD COLDS FROM THE STANDPOINT OF THE INTERNIST: THEIR RESULTS AND TREATMENT.

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Head cold, variously denominated coryza, catarrh, la grippe, etc., is such a common complaint in this latitude that one is almost disposed to think of it as a necessary evil. How few ever consult a physician for this ailment. Yet unquestionably it is the cause of a vast monetary loss as well as an inestimable amount of suffering and pain. In 1911 the Boston Board of Commerce instituted an inquiry into the economic loss of colds, both as to time and money, and the results are rather startling. It was found that one-half of the population of Boston suffer from a cold during six months of the year. One-fifth of the population are absent from work all of the time as a result.

Among six hundred employees of large concerns, such as department stores, there was an average of six days' absence from work in six months as a result of colds, making an economic loss of $21 apiece, exclusive of medical attention. In addition there was a loss of energy amounting usually to $3 apiece, making a $1200 loss. Those from thirty to forty years of age, the most valuable period of life, were the worst sufferers.

By head cold, of course, I do not mean epidemic influenza—real la grippe, with Pfeiffer bacillus—that is an entirely different disease, and I hope that no one will understand that I am discussing it.

As to the cause of most if not all of these colds I think there can be but one answer, and that is that they are infections. When one in a family contracts such an attack, then practically every other member of that household, as well as most of those who come in contact with them, will be affected within a short period. Whether the cause be a coccus or an unfilterable virus, as some think, cannot as yet be determined, but the evidence is overwhelmingly in favor of infection. It is true that draughts, congestion, etc., favor the entrance or at least prepare the soil for the invader, probably already there awaiting for a suitable culture media. That there are certain cases associated with food allergies, such as those following ingestion of eggs, meat, etc., there is not much doubt, but they are in the minority. People of a gouty taint probably acquire them in this manner. Some individuals who have these colds frequently have a chronic sinus that infects the nares at stated intervals, but the majority are contact cases.

In this connection it might be well to state that three years ago, at the suggestion of Dr. Luckett, attending surgeon at the Harlem Hospital, I investigated a series of postoperative pneumonias occurring in the hospital. I found that in every instance the anesthetist or attending nurse—generally the anesthetist—was suffering from an infectious rhinitis, usually of the second type described below. Cultures in a few instances showed pneumococci, but nothing definite was ascertained by culture methods. I have since seen several cases of postoperative pneumonia, and in almost every instance have been able to establish that the anesthetist suffered from a severe head cold. I find that for years the fact has been observed that postoperative pneumonias occur very frequently in groups, which have been charged up to cone infections, etc., but I do not know if anyone has accused the anesthetist before.

In the diagnosis it may be argued that bacteriological examination should be made in each case, inasmuch as there is no agreement as to the exact causative agent, such work would be futile in practice at the present time. Clinically, the vast majority of the cases fall in a few groups, the general character of each being the same but modified by the peculiarity of the individual. At one season one group will prevail, and at another season there will be another picture.

Undoubtedly, there is a definite bacteriological basis for this grouping, but until the matter of origin is settled one must be content to follow a clinical classification.

For purposes of general discussion one may divide these colds into three classes: (1) mild; (2) moderate; (3) descending.

1. *Mild*, with little or no discomfort, limited to the nasal mucous membrane and associated with a watery discharge and slight headache for part of a day, followed by slight mucopurulent discharge; very often this slight discharge is associated with a few drops of blood. After the second or third day the discomfort is scarcely noticeable, and if questioned a week or so later the patient must plainly make an effort to recall the cold and the bleeding. In a fair proportion of these cases, somewhere between the fourth to the eighth day, there develops an attack of muscular pain and soreness —a variously denominated lumbago, stiff neck, pleurodynia, or muscular rheumatism—and, curiously enough, the patient states that he thinks he has taken cold, although apparently he never associates the head cold and the muscular pain. This is somewhat analogous to the nephritis developing three or four weeks after the onset of scarlet fever. In some instances the pain is spontaneous; in others the myositis seems to be present only when the patient makes some sudden effort, as in stooping, etc. These pains persist for a varying period—usually two to five days or more—and then generally, but by no means always, disappear. The head colds contracted in the spring seem to be more commonly followed by these symptoms than those occurring in winter. This pain is evidently due to a toxemia resulting from the nasal infection. After many inquiries I have yet to see an attack of rheumatic fever follow such a cold. Possibly the infecting agent is not sufficiently virulent.

The relation which these backaches and so-called muscular pains bear to nose cold must have been observed an innumerable number of times, yet I am not cognizant that this fact has been pointed out in the literature. It is true that Rosenow believes that he has discovered cocci in the muscles in cases of lumbago, etc., consequent to disease of teeth and tonsils, but I do not find anyone who has done so after a rhinitis and yet there is no reason why they should not be present after such infection. The ache, when it does occur, is evident in nearly every instance before the eighth day from the appearance of the first symptom. Of course, there are plenty of such colds that are never followed by painful attacks, but aside from those aches manifestly due to mechanical causes and gaseous distention, most of the so-called muscular rheumatism will be found to follow within a week or two of a head cold. The chronic cases are doubtless connected with old sinus infections.

Sometimes nerves, such as the sciatic or brachial, are affected, and a true neuritis follows. Since I have thought along these lines, it appears that most of the hitherto unexplained cases of sciatic

and brachial neuritis occurring in hospital practice have followed within a week or so after a catarrhal cold. In two instances, treatment directed to the nasal infection brought about cure after other measures had been absolutely unavailing. It is not intended to maintain that all forms of brachial and sciatic neuritis are due to head colds, but they are at least a frequent cause. In a few cases I have been able to associate a similar relation of cause and effect between the onset of head cold and a phlebitis occurring in the varicose veins of the leg. Whether or not this was only a coincidence, the number of cases has been too small to determine definitely.

2. *The moderately severe cases* begin in the same way as the mild cases, but in a day or two the discharge becomes muco-purulent, and later purulent, often excoriating the skin and mucous membrane; there is loss of the sense of taste and smell, and sometimes marked sinus or middle ear involvement. In the first day or two of these cases, there is usually some muscular soreness and pain, but it is general in character and passes off by the third day. It is not common to find it appearing after the fourth day, as in the mild cases above mentioned, although sometimes it does occur and then it is apt to be very persistent. The total duration of the average case in this group is from ten to twelve days.

3. *The third or descending group* begins as the last-named type, but steadily invades the other tissues farther down: (1) the throat and pharynx, as evidenced by pain and soreness in swallowing, and (2) by the third or fourth day the bronchi are invaded and there is well-marked cough and expectoration. In some individuals this sequence follows every head cold no matter how mild it may be. Most if not all the office cases of bronchitis that one ordinarily sees through the winter season come with just such a history. The symptoms and clinical course of such attacks are so well known that a further description is unnecessary, and it is only mentioned here because it is part and parcel of the head cold, and to point out that its rapid cure depends on treating the original focus of infection in the head.

As has been stated, the average patient rarely consults a physician for a head cold (1) because he has been told so frequently by physicians themselves, or by the altruistic paper-writing physician of the daily press, that there is no cure for this affection; or if he does perchance go to a physician he is usually dismissed with a prescription for some capsules which, on reading, he finds contain phenacetin and aspirin, and he is advised to take quinine or a Dover's powder at bedtime. As a consequence of this advice he does not see much difference in the duration or severity of the attack as treated in this way and when treated according to his own custom, so he does not try again.

Now, while it is true that, excepting those who claim such marvelous results from specific vaccines, there is no one who can claim

a cure for a head cold in the sense of a specific, yet it were just as logical to say that because we have no specific for pneumonia, typhoid fever, etc., that we cannot do anything for them. We can at least lessen symptoms, prevent complications, and hasten recovery. All of these things we can do for head colds, and it is of just as much importance to treat them as the infections mentioned above, because they are of more importance in the aggregate, both as to number and complications, than any other single infection, be it typhoid fever or tuberculosis. This may seem a startling statement, but if one considers their great frequency, the complications—the otitis, mastoiditis, and other sinus involvement—and the disability as already mentioned it will not appear to be an exaggeration.

TREATMENT. There is no sound basis for believing that any of these colds may be aborted, although many have fond delusions of so doing.

Before discussing the special methods of treating it seems proper to discuss the general hygienic measures.

When the patient comes on the first day of the disease the diet should be restricted, *i. e.*, he should strive to get up from the table hungry. Curiously enough, at the commencement of these colds many people have a prodigious appetite. Partaking of large quantities of protein food unquestionably increases the nasal congestion. Purgation early and often should be practised during the first few days, as by its derivative effect the turgescence of the turbinates is markedly lessened, and for that reason the headaches are usually much relieved on free purgation.

Most physicians prescribe one cathartic at the commencement, but it should be repeated on alternate days in cases that do not clear up promptly. A hot mustard foot bath also acts as a derivative, and is particularly valuable on the first and second day of the cold.

The stereotyped advice should always be given to avoid draughts, wet feet, and crowded places. Many a pneumonia has followed in the wake of a coryza after the patient has returned from a theater or other crowded place.

Tobacco must be interdicted for a few days at least. Alcohol in the form of beer, whisky, or rum is absolutely contra-indicated. The old notion that hot toddy helped a cold is due to the fact that the patient forgot his aches and troubles more quickly under the narcotic influence. The sweat and few extra hours in bed undoubtedly make the patient feel better and hasten recovery, but any other diaphoretic agent would do the same, and do it more safely. A hot lemonade is quite as efficacious.

In all disease of the mucous membranes it is a well-known fact that nothing so much impedes recovery as the taking of even small quantities of beer or whisky, and this should be particularly impressed on the patient when such cases do not readily respond to treatment.

*Quinin.* I suppose that two-thirds of the profession prescribe quinin in the early stages of these complaints, and some continue its use throughout. Certainly, there is no agent which so quickly congests the mucous membranes of the tract as quinin, and sometimes even in small doses. One can understand the homeopath prescribing small doses of quinin on the Hahnemannian principle that slight congestion will relieve intense congestion, but from any other view-point it is difficult to see the *rationale* of its action. There are millions who swear by it, as I suppose there were millions who vouched for the value of blood-letting, antimony, etc. Personally, I have never seen any good from its use, although I have used it often and in various doses; and I have often seen harm follow its use.

Dover's powder is still used at the onset, oftentimes with the idea of aborting the cold. Unfortunately, medicines can rarely strangle germs. It is not as popular as it used to be, possibly because more people now seem to be susceptible to the disagreeable after effects of opium than formerly, or because of the anti-opium hysteria which has spread over the country. I have never satisfied myself that its benefits equalled its disadvantages.

Acetyl acid salicylic, I believe, does relieve symptoms, and in small doses it does not congest the mucous membrane seriously. In some patients relief is undoubtedly afforded by atropin. Under the title of rhinitis tablets this medication is much in vogue. The well-known combination of quinin sulphate ($\frac{1}{2}$ grain), fluidextract of belladonna ($\frac{1}{8}$ grain), camphor ($\frac{1}{4}$ grain) makes the practitioner feel that he is orthodox in using quinin and camphor in treating a cold; but it is the atropin that produces the results. The dryness of the mucous membrane that follows its use causes most people, after a time, to discontinue it. In order to obtain good results it must be given early in the attack, *i. e.*, within the first twelve hours, and repeated every half hour or so until the physiological effect is produced. Of course, it does not cure the cold, but it alleviates the most prominent symptoms of coryza during the first day or two. After that the disease runs as before. It is useless in the moderate and descending types of the disease. When the profuse watery discharge is very troublesome a powder consisting of bismuth subnitrate (dr. ij), starch (dr. j), gum arabic (dr. ss), with menthol (gr. ij) or antipyrin (gr. x), may be snuffed up. This almost always gives considerable relief.

Much has been said of the use of vaccines in this complaint, but it is difficult to judge of their effect because the vast majority of the cases are in the very nature of things better before a second injection may be made. If one takes the standard laid down by Wright and his followers, who state that there is no marked improvement in the opsonic index in the vaccinated before a period of from four to seven days afterthe first injection, then by the time the second injection is

due nature has cleared up most of these cases so that it is difficult to decide what effect has been produced. Whether their continued use at the approach of the fall and winter season will prevent subsequent attacks is also a matter that must always be open to question, as nature sometimes herself protects. Personally, my results with vaccines, either as a curative or a prophylactic measure, have not been successful.

Practically all of those who consult a physician for this complaint do not do so until after the second day of its invasion. At this time, again, the hygienic advice mentioned above should always be given. If there be much general soreness or pain, acetphenetiden may be added to the acetyl acid salicylic, but the atropin is useless. However, in these cases the local treatment is by far the most important. It has been my habit to begin with an alkaline spray under fifteen to twenty pounds air pressure. This is always followed by a free exudation of mucus. This is repeated until a mild blowing of the nose is not followed by mucopus.

In very sensitive nostrils a spray of 0.5 per cent. cocain may be employed previously, but I have rarely found it necessary. If there be much headache or face pain an adrenalin spray of $\frac{1}{10000}$ is employed; usually this is not necessary. Ordinarily after the alkaline spray the following spray is used: Acid. carbolic., ♏iij; iodin, kalii iodid., āā gr. vj; aqua menth., glycerin., āā ℥ss; aq., q.s. ad ℥iij. This is sprayed until it reaches the throat.

After this an oil spray is employed for about two minutes. The composition of this oil spray is as follows: Ol. cloves, ♏x; camphomenthol, gr. xxiv; ol. pinus sylvestris, ♏xx; liq. petrolatum, q.s. ad ℥iij.

All of this treatment does not consume more than five minutes when an electric power pump is used.

By these measures one does not intend to destroy all the germs but rather to lessen their virulence and provide drainage, sound surgical measures in any infection. When the infection has traveled to the bronchi these cases are usually treated by various expectorants and narcotics.

No one can gainsay that such expectorant medicines do produce good results in the way of alleviating symptoms and hastening recovery, and they should be always employed, even though their efficiency cannot be determined or proved by animal experiments. Certain it is that if one examines the nose of the average patient who presents this sequence of coryza, tracheitis, and bronchitis he will find there is much inflammatory reaction still present in the nose several days after the nasal symptoms have subsided. In all of these cases of bronchitis, if the nose be treated in the way outlined above in addition to the internal medication by expectorants, the patient recovers in a little over one-half the time that is required when only internal medication is employed.

After a patient has been treated in the manner outlined he volubly expresses the opinion that he feels much better. His efficiency for work has increased for at least that day by about 50 per cent., in many instances by 100 per cent. If he has been accustomed to stay at home during such an attack he is almost always put in a condition to go to business, and so, economically as well as physically, he is the gainer. For this reason he is anxious to be treated daily until recovery has taken place, so that cure is really effected in the sense of freedom from symptoms and ability to do a regular day's work. Furthermore, complications and sequelæ are less likely to occur. As a proof of the efficiency, such a patient nearly always comes back for treatment.

I am perfectly well aware there is nothing original in the use of these measures; that thousands of doctors are and have been using them; but there is a tendency among internists to consider the nose as the exclusive field of the nasal specialist. One reason of this at least is the practitioner's disinclination to perform manual labor. The average internist believes that his duty ends with an examination of the patient, the writing of a prescription, and a linguistic dissertation of greater or less length. He has a horror of getting out of his chair after the examination. Too many are glued to the chair from the start to the finish of a consultation. Next to the alimentary tract the nose is the most frequent avenue of infection in the human body, and the principal evidence of such infection is the symptom coryza. It is just as much the field of the internist to treat such symptoms by local applications as it is to wash out the stomach when necessary for gastric complaints.

Finally, for purposes of discussion, I would like to emphaisze the following conclusions:

1. That there is a special type of head cold that precedes by from four to eight days most, if not all, cases of so-called muscular rheumatism, lumbago, etc., and that this is more satisfactorily treated by treating the original site of infection in the nose than by the usual methods of treatment.

2. That bronchitis following such head colds is likewise more satisfactorily treated by taking care of the original source of infection in the nose.

3. That this field of nasal treatment is quite as much the province of the internist as the use of the stomach pump in gastric lavage.

4. That a fair proportion of postoperative pneumonias is due to infection of the patient by the anesthetist who is suffering from a severe head cold himself.

# THE DIAGNOSIS OF MELANOMA (MELANOTIC SARCOMA) BY MEANS OF THE RESULTANT EFFUSIONS.

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Melanoma, though not a rarity, is a malady of more than passing interest, both clinically and pathologically, and the diagnosis, by no means difficult histologically, is not always recognized without surgical intervention during life. Any method, therefore, which throws light upon its presence without the necessity of an otherwise advisable exploratory operation saves the patient a needless ordeal and is a welcome aid to the internist.

The laboratory findings of the effusions obtained by paracentesis for therapeutic purposes in the two following cases were most significant. In the event that effusions into the pleural and peritoneal sacs as a result of this malady are as frequent as these experiences would indicate, rather than the anomaly that the paucity or absence of references in the literature would suggest, it seems doubly advisable to make note of the results obtained.

The fluid derived from the thorax of Case I was referred to the laboratory of Dr. Charles E. Simon by Dr. R. B. Morris in February, 1915. Dr. Simon has allowed me to report on these findings. The history of the case was obtained through the courtesy of Dr. O. F. Kunkle, and for the gross autopsy findings I am indebted to Dr. Morris, both of Olean, New York. Case II was admitted to the medical division of Mercy Hospital in the service of Dr. Wm. F. Lockwood, to whom I am likewise indebted for permission to report the case. This patient, relieved of his complaint, insisted upon leaving the hospital after a period of a few days, but in conjunction with the findings of the previous proved case the diagnosis of melanoma seems fully warranted.

The fluids in both cases were obtained at times in the clinical course of the disease when there was absence of the usual diagnostic signs, *e. g.*, melanuria, characteristic pigmentation of the skin, or suspicious tumor of the skin or choroid.

Macroscopically the fluids were almost identical in appearance. When agitated they were quite opaque, even in relatively thin layers when viewed by transmitted light. On sedimentating there was a dense dark brick-dust layer at the bottom, while the supernatant fluid, though intensely pigmented, was clear and appeared dark reddish brown in color. The surface layer was slightly iridescent, with a predominant greenish tone. The foam, obtained by shaking, had a tendency to a pinkish hue in Case I and a dirty olive green in

Case II. When the light fell directly upon the fluids in both thick and relatively thin layers it was almost black so intense was the pigmentation. Here too a slight difference was noted, Case I being of a slightly reddish and Case II of a greenish tinge. They appear not unlike crude petroleum with their deceptive play of iridescent colors. In very thin layers viewed by direct light the fluids were reddish to greenish yellow.

The supernatant fluid when tested with a strong solution of ferric chloride showed no reaction for melanogen, but on the addition of bromine water a yellow cheesy precipitate was formed which became much darker on standing, finally becoming almost black, thus indicating that the transformation from melanogen to melanin had been complete *in vivo*. Tests for bile pigments were negative.

Microscopically the sediment showed not only red blood corpuscles, epithelial cells, and numerous leukocytes, but also many tumor cells, which when unstained had the typical pigmented granules of melanoma. These cells were round or oval for the most part, occasionally polygonal; the round or oval nucleus was usually centrally placed, frequently showed mitosis, and occasionally was extruded from the cell; often the nucleus was completely hidden by the closely packed brown granules included in the cytoplasm of the cell; the granules themselves were coarse, irregular in size and shape, and of an intense brown color. When stained the entire cell was basophilic, the granules intensely so. The separate granules were apparently bound together by a delicate basophilic reticulum.

The specific gravity of the fluids varied between 10.24 and 1.030.

Case I.—K. B., a spinster, aged forty years, a saleswoman by occupation, complained of spitting of blood which began about May 1, 1914.

*Family history* was free from tuberculous taint, but her maternal grandmother and one maternal aunt died of cancer.

*Past history* revealed that she had never been robust. She had had the usual diseases of childhood. In 1906 she had what she considered a severe cold, which lasted about two years. After recovery from this she was better than ever before, until October, 1913, she began feeling tired, had no energy, and was bothered considerably with dyspepsia. There was, however, another period of good health which continued up to the onset of the present illness.

*Present Illness.* This began May 1, 1914, with loss of weight, apetite, and energy, soon followed by hemoptysis. After the initial hemoptysis there was daily expectoration of sputum streaked with blood.

*Physical examination* made May 15, 1914, was unimportant, save for the chest. Here there was indefinite impairment of resonance at both apices, slight prolongation of expiration above the clavicles, slight interrupted breathing at the apex of the left lung, numerous fine rales elicited only after cough above the second rib on both

fronts and above the spine of the scapula on the left and a little lower than this on the right behind, and finally an "abnormal" transmission of whispered voice sounds over the dorsal vertebræ.

On these physical findings, together with the history, a diagnosis of early tuberculosis was made involving the apices of both lungs and the mediastinal glands.

*Course of the Disease.* The patient was admitted to a sanatorium June 20, 1914. Her temperature seemed to corroborate the diagnosis of tuberculosis. She improved in every way, with the single exception that she continued to expectorate sputum streaked with blood for a period of eight months subsequent to her admission, despite the usual measures employed for its control. Tuberculin (form not stated) was given in very small doses, with only ephemeral improvement. During these eight months the adventitious sounds in the chest largely disappeared, the rales being practically confined to the apex of the right lung. The sputum was repeatedly examined but never showed any tubercle bacilli, neither were any cells found to suggest malignant disease. December, 1914, a roentgen-ray plate made by Dr. Morris showed slight clouding of the apices. The descending arch of the aorta showed a conspicuous shadow and the mediastinal shadow was slightly broadened. From the root of the left lung, extending downward and blending intimately with the shadow of the heart, was an intense clouding, showing areas through which the light was more readily transmitted. At this time (December 7) hemoglobin was 68 per cent., red cells 6,312,000(?), leukocytes 9200. A differential count was not made. The apices at this time were practically clear, but careful examination over the area corresponding to the shadow of the roentgen-ray plate showed slighty impaired resonance and a few rales. At this time (seven and a half months after the onset of her illness) the patient had gained eight pounds and was a little heavier than her usual weight when in good health. January 6, 1915, the patient felt a slight pain on the left side and a few days later she felt a gurgle within the chest. The day after she experienced some dyspnea. Ten days after the onset of this train of symptoms she showed dulness at the left base with Skodaic resonance above. A spontaneous hydropneumothorax was diagnosed which was confirmed by roentgen ray. Exploratory puncture showed the effusion to be "bloody." Three laboratories reported the fluid to be sterile, without tubercle bacilli and with an absence of malignant cells. Guinea-pigs six weeks after inoculation showed no evidence of disease at autopsy. The cytological examination was essentially that of normal blood. Following the development of the hemopneumothorax, cough, expectoration, and hemoptysis ceased. February 13 paracentesis was done for the relief of pressure symptoms. The pleura at the sixth interspace in the midaxillary line was markedly resistant to the introduction of the needle. Twenty-four ounces of coffee-colored fluid were removed. Subsequently the

rapid reaccumulation of the same character of fluid necessitated aspiration at about five-day intervals. The fluid obtained February 24 was the first which reached us, and has been previously described. A definite diagnosis of melanoma was made at this time. At the site of the puncture of February 13 a metastatic pigmented growth developed within a few weeks. The day following this aspiration the patient developed a fever which continued until the end. The decline from this time was rapid. The patient died April 6, 1915.

*Pathological Findings.* Autopsy performed the day of death by Dr. Morris showed the following points of interest: The left pleural cavity contained a large quantity of bloody fluid, the left lung being compressed into a small space. The right lung was likewise partially compressed. There was no gross lesion suggesting tuberculosis. The heart was completely displaced to the right. Careful examination of the abdominal organs for the primary growth revealed nothing. Save for a general enteroptosis all of the organs were normal. The uterus was infantile and contained a single subserous nodule. The retroperitoneal and mesenteric glands were normal. There was no note of any pigmented moles or of the condition of the eye-grounds. The thoracic viscera together with the uterus were sent to Dr. Simon for examination. The uterine nodule on histological section was a fibromyoma. The hylus of the left lung was almost replaced by a friable, partially necrotic, brown mass invading the parenchyma of the left lung and the visceral pleura. At this point there was direct communication between the pleural cavity and the bronchial tree. The extent of this mass was considerable, involving the major portion of the collapsed left lung. Histological section showed the typical structure and pigmented cells of melanoma.

CASE II.—W. C. P., aged thirty-four years; driver by occupation; admitted to the Mercy Hospital April 5, 1916, complaining of swelling of the abdomen.

*Family History.* Mother and one maternal uncle died of tuberculosis many years ago. There was no history of malignancy. One child died shortly after birth. It had a spina bifida. Otherwise the family history was without interest.

*Personal History.* Patient's health has always been good. Save for measles and mumps during childhood he has never had any illness. His habits were bad. He smoked from twenty-five to thirty cigarettes a day and for many years he has drunk fifteen or more glasses of beer daily. In addition he has occasionally gone on a spree, when whisky and gin were taken. His occupation exposes him to all sorts of weather. He denied venereal infection (the Wassermann reaction was negative).

*Present Illness.* This began eight months before admission with gradual abdominal enlargement. For the first four months there was no pain and the patient thought he was getting fat. Four months ago he began to experience pain in the lower left quadrant,

intermittent in character and exaggerated on standing and walking or on eating or drinking. At this time the distention was as marked as on admission. He entered the hospital for an accentuation of the pain in the lower left quadrant.

*Physical Examination.* The patient, a marked brunette of medium build and well-nourished, showed slight dyspnea. The skin, though dark and slightly sallow, showed no jaundice or other abnormal pigmentation. The conjunctivæ and mucous membranes were of normal color. The eyes were not prominent, vision was normal and the pupils in every way normal except being slightly dilated. Pulse, respiration, and temperature were normal. The glandular system was normal. The thorax, save for the upward displacement of its viscera, was unimportant. The abdominal distention gave rise to shallow respirations, decreased vocal fremitus at the bases, with impairment of the percussion note over the same and diminished breath sounds over these regions. The P. M. I. was in the fourth interspace 1 cm. inside the nipple line and the hepatic dulness began in the fifth interspace in the right mammillary line, merging with the general abdominal dulness below. The outline of the spleen was obliterated by abdominal dulness. The abdomen was markedly distended, symmetrical, and dome-shaped. The epigastric veins were markedly distended, but there was no caput medusæ. Numerous striæ covered the entire abdomen. The distention was so great that none of the underlying organs were palpable even on dipping sharply with the palpating fingers. Dulness extended over the entire abdomen except for a small area in the lower left quadrant, where the note was tympanitic. There was no shifting in the location of dulness or tympany upon turning to either side or when the hips were elevated. Distinct fluctuation was elicited, the impulse wave being sharp, quick, and rebounding in character. The genitalia and extremities were in no way abnormal. Total red cells were 5,864,000, leukocytes 14,000, small lymphocytes 10 per cent., large monos. 12 per cent., polys. 75 per cent., and eosinophiles 3 per cent. The urine contained a trace of albumin and numerous hyaline and granular casts. There was an absence of bile. The urine did not turn dark on standing nor was melanogen or melanin present by chemical tests.

*Course of the Disease.* Paracentesis was performed April 9, 1916. About 3 liters of coffee-colored fluid were withdrawn. This contained numerous melanoma cells and a few eosinophiles and epithelial cells. Neutrophiles and lymphocytes were in about equal numbers. There were numerous erythrocytes present.

Two days after paracentesis the patient felt entirely relieved. Examination of the eye-grounds at this time showed the disk, vessels and maculæ normal. Through the retina the choroid showed diffusely dark, but not more so than the patient's complexion justified. No tumor was observed. The skin, uniformly dark, showed

numerous small pigmented moles of medium dark color. Over the right posterior-superior spine of the ilium was an absolutely black mole, split pea in size, slightly elevated, with the margin circumscribed and apparently not invasive. The thoracic viscera were in normal position. The abdomen, now scaphoid, had flabby walls. The note all over the abdomen was tympanitic save in the upper right quadrant, where it was quite flat and did not shift with change of position or with respiration.

Here too a small, firm, indefinite mass was felt which was apparently attached to the parietal wall. Neither kidney was felt nor was the edge of the liver palpable. The following day the patient, relieved of his discomfort, insisted upon leaving the hospital.

Conclusions. The character of the two fluids obtained from the cases here described were so nearly identical in gross appearance, chemical reactions, and the microscopic appearance of the sediments that the unconfirmed diagnosis in the second case seems hardly open to doubt.

In the two cases here diagnosed the character of the effusion was the sole clue to the nature of the malady at the time it furnished evidence of the disease.

It is reasonable to suppose that visceral melanoma is not infrequently associated with effusion, and that a study of its character will be helpful in the diagnosis of other doubtful cases.

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## THE EFFECT OF CASTRATION UPON OSTEOMALACIA IN THE MALE.[1]

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and
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Chicago.

The case presented is of interest because osteomalacia in males is a rare condition. It is of interest also, because, while the operation has long been suggested, there is no other report, as far as we know, of a male patient treated by castration. This patient has been under observation long enough to warrant some conclusions as to the probable effect of castration.

Dock found reported in this country, up to 1895, only 11 cases of osteomalacia, all in females. Hahn, in 1899, was able to collect from the literature 42 cases in males, but the diagnosis of some of these is in doubt. McCrudden, in 1910, stated that among 360 cases of osteomalacia reported by five writers, 39 were in men.

[1] Presented to the Chicago Society of Internal Medicine, May 22, 1916.

Without making a special search he found reported in the last twenty-five years 10 cases in unmarried females and 9 cases in males. In 4 of the latter the diagnosis was confirmed by necropsy.

CASE HISTORY. The patient, aged thirty-four years, first came under observation in October, 1910. At that time he complained of pain in the hips, groin, and heels.

FIG. 1.—Patient at time of first examination, October, 1910.

FIG. 2.—Five years after operation August, 1916.

In 1906 and 1907, while training for a wrestling match, he noticed a soreness across the chest and an unusual shortness of breath after running. He had previously been perfectly well. On March 17, 1907, he was thrown in a match by a scissors hold. The squeezing of his chest caused excruciating pain. In July, while working on a farm, it was remarked that the bib of his overalls seemed pushed forward. Later, he noticed stiffness and tender-

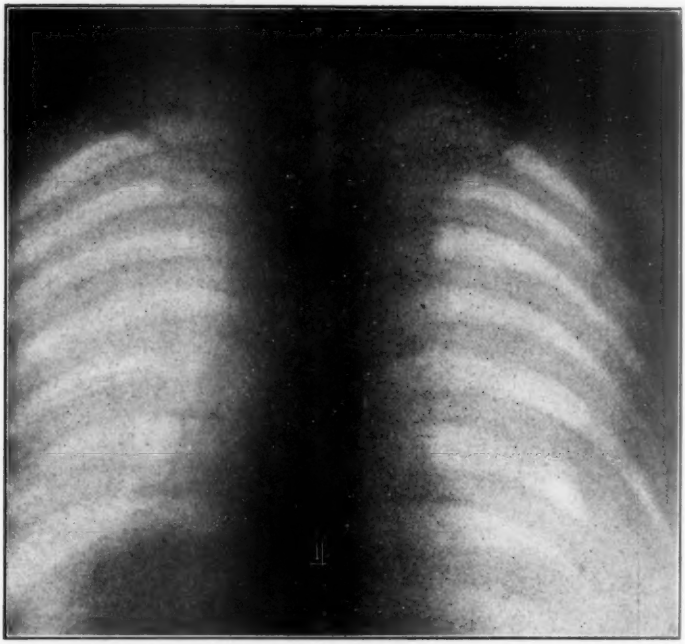

FIG. 3.—Chest radiogram, October, 1910. Note the apparently poor radiogram due to the loss of lime deposit.

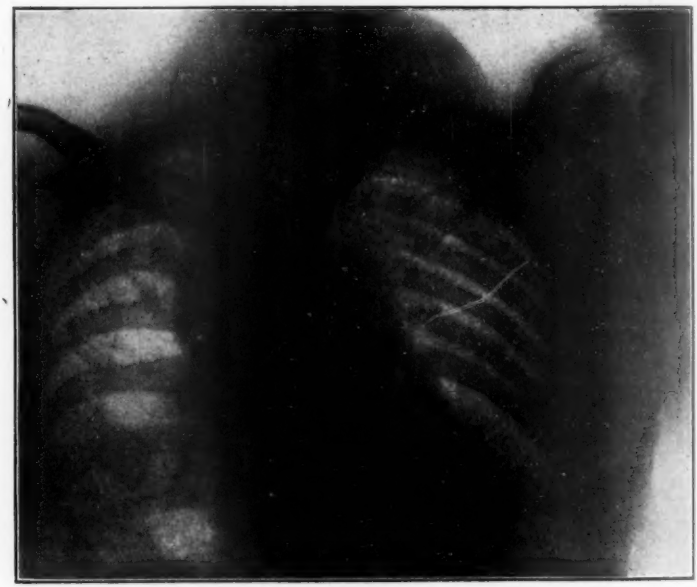

FIG. 4.—Chest radiogram, November, 1913

ness of both Achilles' tendons. In the summer of 1908 the heels felt bruised and sore. He was treated for flat-foot and rheumatism, without relief. At this time, although he seemed aware of a deformity, the chest was pronounced normal by several examiners. After seven months the knees became painful and two months later the hips were affected. There was pain in the upper thigh, especially upon rising from a sitting position. During this period the patient performed hard manual work, in the hope of regaining his health. After some months the chest became noticeably deformed. He was unable to stoop because of pain in the hips. He could not rise without the aid of his hands.

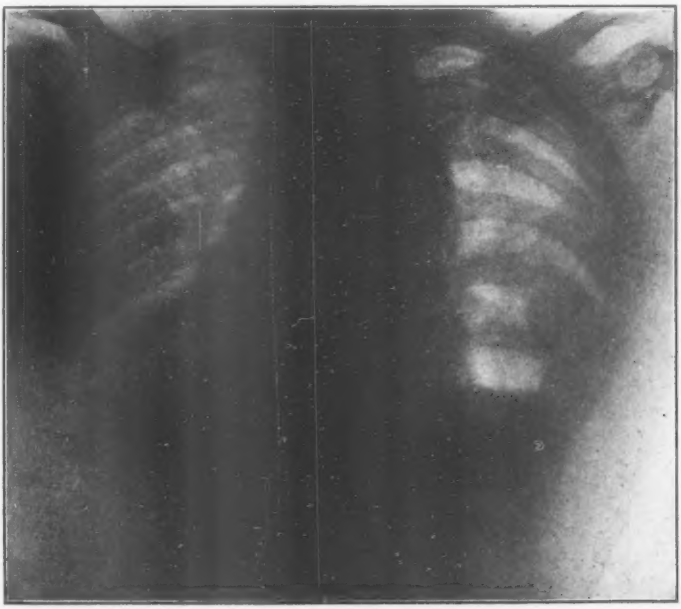

FIG. 5.—Chest radiogram, May, 1916.

There was no family history of deformity, goitre, tuberculosis, or malignancy. The patient had measles at four years, followed by whooping-cough. He had no fractured bones except a broken clavicle in infancy. He denied venereal infection. There had never been much hair upon his face or body; he needed to shave only once in two weeks.

The patient had been an athlete since the age of thirteen years. From 1904 to 1907 he was in the United States Army, chiefly as cook. He became a professional wrestler; he boxed and wrestled frequently. He could raise 500 pounds above his head. When

nineteen years he stood 5 feet $11\frac{3}{4}$ inches in his bare feet and weighed 160 pounds.

When first examined, in 1910, the patient was fairly well nourished and weighed 127 pounds. He had moderate general adenopathy. The chest showed great prominence anteriorly with lateral compression (pigeon breast). Marked angulation at the level of the sixth and seventh vertebræ. The ribs were very pliable and could be pressed back into the normal anteroposterior position.

FIG. 6.—Region of the knee-joint. Radiogram of December, 1912.

The iliac bones were very tender. Intense pain was produced by pushing together the iliac crests. Both heel bones were tender.

No other abnormalities were found. Blood and urine were normal; the Wassermann test was negative. Radiograms showed a characteristic loss of bone markings and mineral deposit as well as chest deformity.

Treatment with phosphorus was begun and was followed for over three years. Thyroid extract, pituitrin, Fowler's solution, green vegetable diet, and adrenalin caused no improvement. On

the contrary the bones remained soft and tender and the chest deformity increased. In June, 1911, both testes were removed by Dr. Allen B. Kanavel. They were reported normal grossly and histologically. Examination of the urine and feces showed, contrary to expectation, an increased elimination of CaO and $P_2O_5$ in the days following as compared with the days immediately preceding operation.

FIG. 7.—Region of the knee-joint, May, 1916.

Six months after operation the patient felt well, but the chest deformity had reached a high grade. After fourteen months, while on thyroid extract treatment, he became very nervous and developed a tremor which has persisted. There had been no tremor before this time. One year after operation the bones seemed harder. Sugar tolerance was increased, elimination following the feeding of 124 grams of glucose.

In 1913 there was less pain and the patient was able to walk five blocks without difficulty. His height was 5 feet 5 inches. He stood several inches taller in the morning than at night. Radio-

grams showed increased chest deformity and no improvement in bone structure. In 1914 nervousness and tremor increased. Since 1915, when medication was stopped, he has used a crutch and a cane for the relief of pain in walking.

FIG. 8.—Region of the elbow-joint, October, 1910.

At the present time the patient states that he has recovered from his former "lost" feeling. He dates the improvement from six months after operation. The pain in the knees has persisted. There have been no signs or symptoms of stones in the urinary

tract. The thyroid is small; the palpebral fissures seem wide; a fine tremor is present. There is a moderate secondary anemia. Temperature has been normal throughout the course. No foci of infection have been found. While the bones seem harder, radio-

FIG. 9.—Region of the elbow-joint, November, 1913.

grams show no improvement in the general structure but rather an increased porosity. The skull bones participate in the loss of mineral deposit; the sella turcica is small.

The case presented is one of osteomalacia of the type designated

metaplastic malacia or fibrous osteitis by von Recklinghausen, who suggests an analogy to inflammatory fibrous tissue produced in chronic myocarditis and hepatitis.

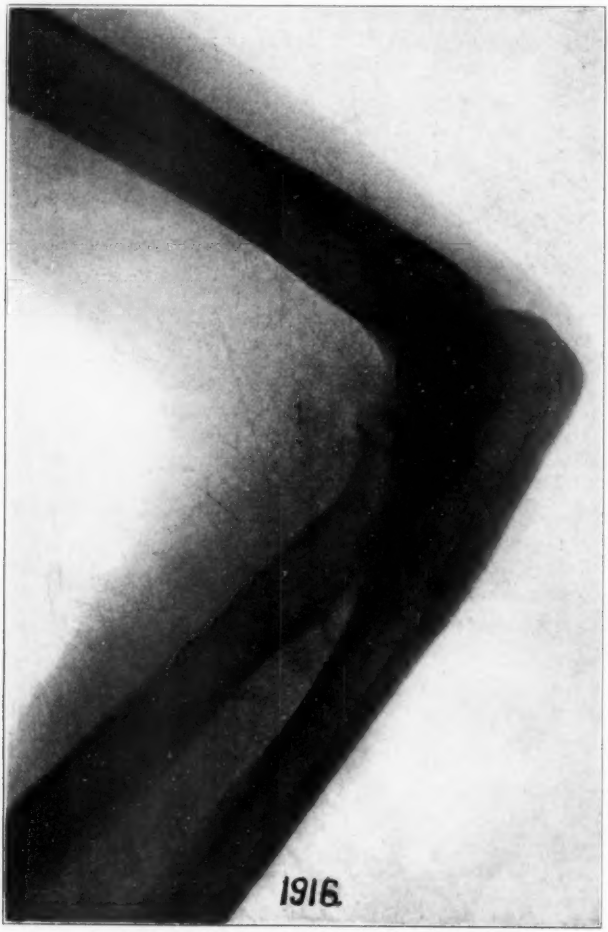


FIG. 10.—Region of the elbow-joint, May, 1916.

In this case the process seems to have begun nine to ten years ago in the vertebral column, although very early there were symptoms which led to the diagnosis of "rheumatism." The early involvement of all the bones is characteristic of male osteomalacia. As in the other cases reported there was no response to the usual methods of treatment.

A possible etiological factor in this case was the injury to bones incurred in boxing and wrestling. Such injuries, not severe enough to cause fractures, may, according to McCrudden, be sufficient to upset the balance of bone metabolism. There has been no evidence of disturbed internal secretion beyond increased sugar tolerance and rapid development of a persistent tremor after a short course of thyroid extract.

In spite of progressive chest deformity and unimproved bone structure, the possibility of a remission is suggested by the prolonged course, the confinement of deformity to the vertebral column, and the clinical improvement in the hardness of bone and in general well-being. According to Tinz, spontaneous cure or arrest of the process has not been noted in male cases. Berger describes an apparent remission in a case after extreme deformity of chest and extremities had developed. In the case presented castration may have helped to exert a favorable influence.

The cause of osteomalacia is not known. The disease has been attributed to infection, errors of nutrition, and perverted glandular function. Organisms have been isolated from the blood of patients and of animals suffering with a similar condition. Organisms isolated from the blood of white rats have reproduced malacia after injection into other rats. Feeding experiments have suggested the relation of errors of nutrition. The theory of perverted glandular function has been most supported, and much work has been done in the attempt to fix the responsibility of the various ductless glands. The ovaries, hypophysis, adrenals, thyroid, and parathyroids have been thought to play a role, singly or as a part of a polyglandular syndrome.

The loss of calcium and the softening of bone, together with a new production of bone poor in lime are characteristic. There is a tendency to lime deposit elsewhere, as in the kidneys and bladder. McCrudden believes that osteomalacia is an exaggeration of a normal function, that the balance of bone metabolism is disturbed by excessive demands for calcium, as in pregnancies, bone tumors, and fractures. When bone katabolism exceeds anabolism the result is osteomalacia.

Treatment is empirical. Phosphorus, adrenalin, pituitrin, thyroid extract, arsenic, chloral, and chloroform narcosis have been among the remedies advocated. Since Fehling, in 1887, recommended castration in the treatment of osteomalacia in women, authors have reported as high as 80 per cent. of cures following operation. Sterilization by Roentgen rays has proved beneficial. Results were best in puerperal cases, which often tended to recover spontaneously; nulliparæ were usually not benefited. Metabolic studies do not indicate that a mineral retention is produced after castration, as was supposed. Accordingly, many authors believe that the value of castration and sterilization lies only in the pre-

vention of future pregnancies. Although castration of male cases has been advised in the hope of producing results comparable with those reported in female cases, no report of the operation has been found in the literature.

CONCLUSIONS. Five years after castration the case reported shows no actual improvement in bone structure. A probable remission has occurred, which may have been influenced by the operation. The result of castration in this patient would seem to indicate that osteomalacia is not a disease of the sexual glands.

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## AUTOINTOXICATION AND ITS TREATMENT BY (TRANS-) DUODENAL LAVAGE.

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AUTOINTOXICATION is a toxic condition of the blood and lymph caused by substances generated through the influences of the vital processes of the organism.

Autointoxication occurs in two forms: (1) the histogenic, and (2) the enterogenic. The histogenic is due to abnormal function of the antitoxic glands and of the tissues; the enterogenic is caused by abnormal action of the digestive enzymes and of the bacteria upon the food. The result of this action is the generation of numerous poisons and noxious substances, which, unless neutralized or removed, are absorbed into and circulate in the blood and at length give rise to autointoxication.

As the vitiated blood reaches everywhere, any part of the body may become diseased through the influence of the circulating toxins, which manifests itself generally or in ways peculiar to the affected organ or tissue; for instance, as anemia, general malaise, migraine, facial neuralgia, nervousness, melancholia or other psychoses, goiter, circulatory disturbances, bronchial asthma, catarrh of the mucous membranes of the respiratory or digestive tracts or of the liver, attacks of vomiting or diarrhea, albumin or sugar in the urine, rheumatism, cutaneous outbreaks and in many other ways.

Clinically, the presence of excessive putrefaction, excessive fermentation, an acid reaction of the stool, or a combination of any of these is suggestive of some form of enterogenic autointoxication.

The diagnosis of the putrefaction of proteids is readily made by the indican test, but about the decomposition products of excessive carbohydrate fermentative and of faulty fat digestion so little is known, and they are so hard to trace except when abundant enough to cause acid stools, that this condition is rarely recognized, which naturally leaves much undone by way of treatment. The difficulty of dosing these toxins and the ease of making the indican test have caused the term autointoxication to become practically synonymous with putrefaction; but it is precisely the toxins from carbohydrate fermentation and faulty fat digestion, especially the volatile fatty acids, and of these more particularly lactic, acetic, and butyric acid, which constitute a potent cause of disease by lowering the alkalinity of the blood and lymph, acidosis so called.

The bacterial count, too, is uncertain and misleading as an index to autointoxication, for while the estimated normal of 125,000,000 bacteria in the daily stool is found much increased in simple fermentation with a corresponding increase in the proportion of the intestinal toxemia, their number may be greatly reduced if large amounts of chemical toxins, poisonous to them, are present (see Case VII).

As in chronic morphin poisoning, so in both histogenic and enterogenic autointoxication the gastro-intestinal tract is the principal channel of elimination for the toxins circulating in the blood.

Of the various methods of treatment the Metchnikoff and the elimination treatment are those most generally employed at the present time. The Metchnikoff treatment consists in making of

the intestinal contents a culture medium for the Bacillus bulgaricus, which, through the formation of lactic acid, creates an environment in which the putrefactive bacteria can no longer thrive. As a rule it quickly reduces the evidence of pure alkaline putrefaction, but is obviously contra-indicated whenever the volatile fatty acids or their derivatives are at fault. The elimination treatment consists in purgation and in colon irrigation; both give some relief, but purgatives are irritant and contra-indicated as a routine measure and colon irrigation cleanses at best only the large bowel.

Therefore, considering that it is unscientific to further increase the volatile fatty acids by the Bacillus bulgaricus treatment if they are already present in excess; that because of the difficulty and cost a thorough chemical stool examination though almost indispensible for proper treatment can rarely be made; that the circulating toxins are chiefly discharged into the intestine, and, finally, that purgation and colon irrigation are of limited usefulness, a wide application should await a method of treatment which because of its efficacy in all cases of autointoxication makes a complicated feces analysis in most cases unnecessary, and which combines all the good features but has none of the disadvantages of the Metchnikoff treatment, purgation, and colon irrigation. Such a method is (trans-)duodenal lavage, first described by the author.[1]

Duodenal lavage flushes out the entire length of the intestinal canal from pylorus to rectum; it bodily removes the toxins of whatever nature; it restores by simple cleanliness in the intestinal tract the conditions necessary for normal bacterial growth, as shown by the results obtained; in this way it lays the foundation upon which the curative forces of nature may build the structure of returning health.

For duodenal lavage to be effective the irrigating solution must be non-absorbable; it must be employed in bulk and be sufficient in volume to flush the bowels. Further, because of the taste, the intolerance of the stomach to the amount of solution employed and the necessity of overcoming the control of the pylorus, the solution must be introduced directly into the duodenum, which is accomplished by means of a duodenal tube.

The treatment is easy to take if skilfully given; it consumes only about fifteen minutes, and is followed within an hour by from one to three pleasant watery evacuations, the patient feeling light, free, and buoyant. No untoward effects have ever been observed.

The writer uses a duodenal tube which can be manually introduced, and which, because of its small sinker, slips into and out of the duodenum easily, without the delay incidental to the ordinary

[1] Jutte, M. E.: Transduodenal Lavage; a New Method in the Treatment of Chronic Ailments, with Report of Results in Cases of Asthma and Pernicious Anemia, New York Med. Jour., March 16, 1912. Transduodenal Lavage: Treatment and Report of Some Cases of Chronic Diseases. Jour. Am. Med. Assn., February 22, 1913, lx, 586 and 587.

types of duodenal tubes. This invaluable fact permits the treatment to be carried out as a routine measure in the doctor's office.

A solution which usually passes through the bowel without being absorbed by the mucous membrane is one quart of water containing 9 grams each of sodium chloride and sodium sulphate. To make sure that the fluid will be passed on without being absorbed it is sometimes well to add a small quantity of saturated solution of phenolphthalein. Other medication may be added if indicated, such as sodium bicarbonate in acidosis, quinin in amebic dysentery, powdered medicinal soap (8 grains) in pancreatic insufficiency, resorcin in fermentation, chamomile tea for inflamed mucus surfaces. If silver solutions are indicated the sodium chloride should be replaced by an additional quantity of sodium sulphate.

The method of administration, improved in several details, is as follows: Prepare 1 quart of the solution at a temperature of 105° to 110° F. Moisten the tube and lubricate the interior by forcing a

Author's duodenal tube, with suction bottle.

dram of glycerin into it with a hypodermic syringe. Insert obturator to bottom of hollow stem of sinker. Protect patient's clothing with a rubber apron.

If the patient is nervous, spray the throat with a 1 per cent. cocain solution. The stomach must be empty. Then place the end of the tube on the back of the tongue; the patient should be told to swallow once, at which moment the tube is readily thrust over the root of the tongue. Then, during respiration and aided by occasional sips of water, gently finish the introduction of the tube to the 3-ring mark, step by step, with drawing the wire gradually. Permit the patient to lie down on a couch and turn well on his right side; connect the tube with a suction bottle, and after a minute or so exhaust the air from the bottle with a large size syringe.

The fluid returned becomes stringy the moment the sinker has passed the pylorus and struck enteric secretion, which occurs usually within one or two minutes. With a little practice this moment is easily ascertained, though the stringiness may be very slight.

Let the patient sit up; disconnect bottle and connect tube with container after discarding cooled-off fluid in leader. Let one and a half to two pints run in at a quick drip during from five to ten minutes. A momentary discomfort calls for a short pause. A tapered glass tip inserted in the connecting tube will regulate the rate of drip nicely. When finished let just enough plain warm water run through to rinse the tube. Withdraw tube gently during respiration.

To make the following case reports complete I must mention that in Cases VII to X, in which there was suspicion of excessive carbohydrate fermentation or faulty fat digestion, I withdrew carbohydrates and fats entirely and employed for a time the Salisbury diet, which consists chiefly in scraped or minced lean beef broiled, with plenty of warm water to drink between meals.

Of drugs, digestive mixtures, bile and pancreatic extracts, only were used.

The number and frequency of treatments depend on the severity of the case; in the average case I give the treatment every three or four days for one or two weeks, then weekly for one to three months, and after that at longer intervals.

The following cases, together with those of pernicious anemia, asthma, chronic bronchitis, jaundice, enteritis, etc., already reported, will give a fairly good idea of the wide field for the treatment:

Case I.—Mrs. T., aged thirty years. A case of ptomain poisoning; had vomited numberless times during twenty-four hours. After a few hours of sedative treatment, patient managed to retain duodenal tube and take the lavage. Immediate and complete recovery after bowels had been flushed.

Case II.—Mrs. D., aged twenyt-two years. Goiter, more prominent on right side; slight exophthalmos and severe cardiac and nervous symptoms. Received lavage about once a week for three months. Diet restricted to plain food. The goiter has come down in size gradually, and all the symptoms have uniformly improved.

Case III.—Mrs. G., aged thirty-eight years. A case of chronic headache and general malaise. Had taken every kind of treatment without avail. For personal reasons treatment was crowded, so that within four weeks she received twenty-one lavages, ten thermopenetration treatments of the abdomen and ten injections of polyglandular extract. Improved steadily and markedly, with two slight attacks owing to indiscretion of diet.

Case IV.—Mr. C., aged forty-six years; merchant. Had suffered for six weeks from diarrhea with loss of strength; extreme indicanuria. Had been confined to bed for several weeks. Duodenal lavage was given on eight consecutive days, then for two and a half months every second to fifth day, in all twenty-seven times. The indicanuria was unusually stubborn, the last trace disappearing not until

eighteen treatments had been given. After the first lavage a large round worm was expelled.

CASE V.—Mrs. S., aged fifty-eight years. A chronic case of "biliousness," accompanied by glossitis; skin was of a yellowish, unhealthy appearance. Received lavage once every five days to two weeks during three months; also vibration over the liver. The biliousness improved steadily from the beginning, the skin cleared up, and the glossitis had almost disappeared when seen last.

CASE VI.—Mrs. N., aged thirty-five years. Had suffered for six years from "biliousness," cholecystitis, general discomfort in hypogastrium, and had been for a long time on an ulcer diet; this was discontinued. Received eight lavages within two weeks. Marked progressive improvement in all her symptoms after the first treatment.

CASE VII.—Mrs. D., aged seventy-four years. Found patient suffering from paroxysmal tachycardia with a pulse of about 200, reflexly from gas pressure. Examination of urine and stool showed indican normal, excessive fermentation, enteritis, pancreatitis with inhibition of fat digestion, and autointoxication, due to carbohydrates and fats, with a coefficient of 800 to 100 (von Oefele), the bacteria being reduced to one-eighth of the normal. The acute condition was relieved by emptying the stomach and by a purgative. Another acute attack occurred three days later. A few days after that lavage treatment was commenced at the rate of once or twice a week, in all thirteen treatments. All fats and fermentative food were withdrawn. Much relieved from the beginning. After a few treatments the patient felt quite well, though at first there were occasional attacks of palpitation which finally disappeared. A subsequent stool examination showed a very great improvement in all respects.

CASE VIII.—Mrs. H., aged forty-two years. Had a very severe case of mucous colitis and had been under medical care for seven years; in bed for periods of months at a time on account of hemorrhages. Passed large amounts of jelly-like mucus. In May, 1915, received a daily lavage for five consecutive days; then one every second day for two and a half weeks; after that one every week or two. No drugs were given. From the beginning her condition improved rapidly, so that after a month she felt "fine;" no more hemorrhages have occurred. Takes treatment now merely to avoid recurrence.

CASE IX.—Mr. S., aged thirty-eight years; minister. Had suffered for eighteen years from bronchial asthma and general catarrhal condition of mucous membranes; also for fourteen years from a severe case of psoriasis, especially on face and chest. No previous treatment had availed anything, but camp life during the Spanish-American War had benefited him greatly for a time. Received lavage irregularly during eight weeks, in all about twelve times.

Improvement steady, so that he considered himself cured and finally discontinued visits. The psoriasis, too, paled away and disappeared, except for a few scales here and there.

CASE X.—Mr. B., aged sixty years; druggist. Complained for years of severe flatulence and almost constant tenesmus, with passages of small quantities of mucus and thin fermentative material; very nervous, wornout, dizzy; sallow complexion. Also nails coarsely ridged, extensively undermined and hanging on merely by the roots. Received lavage twelve times in one month; cut out all fermentative food. Improvement immediate, with eventual cure. The nails, too, showed an unexpected and rapid improvement, growing up on a rosy, healthy looking base.

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## COMPARATIVE STUDY OF THE TOXIC EFFECTS OF THE NATURAL AND SYNTHETIC SALICYLIC ACIDS.

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THE task which we originally proposed to ourselves in designing this series of experiments was that we should try to determine the toxic and fatal doses of the natural and synthetic acids and their salts. It was intended to present a brief view of this problem, molded by the inherent constitution of the two drugs. The clinical matter was dealt with only so far as it seemed to throw light on the relation of chemical structure to therapeutic or toxic effects; but it has been found necessary to make greater use of clinical observations, and to treat the whole subject in an evolutionary manner. We will begin with a brief statement of the theme.

Salicylic acid prepared from oil of wintergreen is slightly milder than salicylic acid prepared in other ways. This fact was noticed by Stokvis in 1896, but the discrepancy has remained unexplained, and, indeed, practically undiscussed by chemists and physiologists of late years.

In order to institute a comparison we have examined the acids and their sodium salts, which are to be easily procured, and we have made some clinical studies of the action of the following substances which may be described as complementary: Cinnamate of sodium, phthalic acid, saligenin, salicin, methyl salicylate. The principle recently elaborated by Zadek, who adopted it from Stricker, is one which we have followed. This principle is that salicylic acid is

the ultimate result of any reaction in the body in which these allied substances are concerned.

Comparisons between the two have been instituted by pharmacologists. Studies of this nature have been published by Waddell, Hewlett, Eggleston, and Hanzlik. Intelligent review of these papers is not easy; in much they may be sound, but a strong bias is manifest in all of them.

The dispute over the virtues of natural and synethetic salicylic acids has always been confined to America, and its consequences remain, so far as truth and science are concerned, in an undoubted exacerbation of medical jealousy and a rapid growth of prejudice and ignorance. European writers have not disputed over a subject which is, or ought to be, purely scientific. Probably they have not thought it worth while.

Stokvis gives a fair summary of the science. We have found it accurate, the only point of difference being that salicylic acid is today manufactured with more skill than it was in 1896. But whether the samples which are sold are still free from the injurious cresols and the therapeutically useless parahydroxy benzoic acid is a matter of doubt.

The specimens examined by Stokvis were analyzed by Van't Hoff, and were presumably pure. He tried three acids: one prepared from oil of gaultheria, one prepared from anthranilic acid, and one prepared from phenol. They were similar in all respects. As our results have agreed with those of Stokvis, we tested our samples in the same way.

Fischer states[1] that pure natural salicylic acid melts at 156.8° C., while commercial acid melts at 153.5° C.

According to Bloch,[2] even a small proportion of creosotic acid lowers the melting-point of natural and synthetic salicylic acids. We found:

Purity of the salicylic acids used as determined by titration with $\frac{N}{10}$ KOH: Natural, 98 per cent.; synthetic, 98.64 per cent. These acids were recrystallized three times from hot water and melting-points taken of each crystallization as follows:

| | Natural. | Synthetic. |
|---|---|---|
| Original acid . . . . . | 156.2° to 157.8° | 155.9° to 157.1° |
| First recrystallization . . | 156.2° to 157.7° | 156.2° to 157.5° |
| Second recrystallization . . | 156.8° to 157.8° | 156.8° to 158.0° |
| Third recrystallization . . | 156.8° to 158.0° | 156.8° to 158.0° |

Salicylic acid does not melt sharply. The temperatures given here are the points where (1) the acid fuses sufficiently to flow, and (2) fusion is complete. According to Smith[3] the melting-point of the synthetic acid is 158.5.

[1] Pharm. Zentralbl., xlii, S. 327.
[2] Pharm. Jour., 1890, lxxii, 429.
[3] Ibid., 1915, p. 617.

The original acids were sublimed, sublimates being taken at intervals. The recrystallized acids (third recrystallation) were also sublimed. Their melting-points were as follows:

| | Natural. | Synthetic. |
|---|---|---|
| First sublimate | 155.8° to 157.0° | 156.0° to 156.8° |
| Second sublimate | 156.0° to 156.8° | 156.0° to 156.8° |
| Recrystallized | 156.0° to 156.9° | 156.0° to 156.7° |

The lower melting-points of the sublimed acids are no doubt due to a slight decomposition into phenol, the presence of which tends to lower the melting-point.

Solutions of sodium salicylate (25 per cent.) were prepared by dissolving the acids, together with sodium bicarbonate, in molecular proportions as follows:

| | | |
|---|---|---|
| Salicylic acid, natural (98 per cent.) | | 22.0050 |
| Sodium bicarbonate (99.7 per cent.) | | 13.1624 |
| Water | q. s. to make | 100.0 c.c. |
| Salicylic acid, synthetic (98.64 per cent.) | | 21.8622 |
| Sodium bicarbonate (99.7 per cent.) | | 13.1624 |
| Water | q. s. to make | 100.0 c.c. |
| Sodium salicylate, natural (25 per cent.). | | |
| Sodium salicylate, synthetic (25 per cent.). | | |
| Specific gravity at 20° C. | 1.10276 | 1.10275 |
| Optical rotation | 0° | 0° |

It may, therefore, be concluded that we are dealing with the same chemical structures. The following is a summary of Stokvis's papers:

Charteris and Maclennan showed a considerable difference between the acid prepared from oil of gaultheria and the synthetic acid. The results led both authors to the conclusion that the artificial acid, in spite of chemical purity, for no cresols were found, must be ranked as a physiologically impure substance. In comparing salicylic acids made from phenol with that prepared in other ways, we, of course, included the natural acid. As the interest of the subject is chiefly theoretical, we instituted our comparison by the experimental method. The phenol salicylic acids used, the anthranilic acid, and the acid prepared from oil of gaultheria are chemically the same. Solubility, elementary analysis, and polarization as tested in the laboratory of Van't Hoff, gave the same results. The molecular arrangement of three acids was identical, which would imply physiological identity. But in the animal experiment the case was different.

Sodium salicylate was used in all experiments. They fell into three parts: excretion and changes in the urine, the toxic and lethal doses, the physiological action in men.

The acid prepared from oil of gaultheria manifested a more rapid rate of excretion.

The cause of this quicker excretion is twofold: The natural acid is less active than the others. In rabbits, clear signs of poisoning appeared after large doses, 700 to 800 mg., the fatal dose being 1300 to 1400 mg. per kilogram of the animal's weight. Toxic effects were manifested by profound disturbance of the central nervous system and respiration, paralysis of the hind legs, dyspnea, stupor. Of great interest is the fact that the acid prepared from oil of gaultheria produced almost no tremor, which, however, in the case of the other acids, appeared constantly after doses of 700 to 900 mg., together with convulsions. These toxic symptoms were entirely wanting to the action of the gaultheria acid. Given the same animal and the same doses there was less disorder after the natural acid. The fatal dose, however, of the three acids was nearly the same.

As an extension of these researches, Dr. Morel undertook some on himself. The effects on pulse, temperature, appetite, and other functions were less marked in the case of the acid prepared from gaultheria. The rate of breathing was constantly raised by the phenol and anthranilic acids, but the natural acid caused virtually no change in the respiration.

It appears from these researches that the quantitative difference between the acids is so clearly demonstrated that we must agree wholly with the conclusion of Charteris and Maclennan when they pronounce the natural acid less toxic. To explain this difference, one must consider the greater ratio of excretion of the natural acid, which is due to the greater osmotic properties.

This is not only a sufficiently complete account, for practical purposes, of the systematic side of the subject, but is full of precisely that relation of the living organism to the chemical structure of the drug employed which can be treated properly only by a writer who knows chemistry and physiology, but has a great practical knowledge of the difference between the animals themselves. Rabbits and guinea-pigs are less sensitive than dogs, and dogs less sensitive than men, while human beings in health and disease show marked variations of physiological response to the salicylates.

In the following experiments we began with the intravenous method of injection, next we undertook subcutaneous injection, and lastly administration by the stomach tube. Clinical observations extending over many years are introduced, but in the form of a summary, as it would be impossible to report them in detail. They are introduced merely for the purpose of throwing light on the toxic and fatal doses of the various salicylates.

Injections of sodium salicylate under the skin are very painful, while it is most difficult to inject solutions of the salicylic acids into the veins. It was found that alcoholic solutions caused necrosis at

the point of the injection into the ear vein of rabbits. In intravenous injection the formula cited by Hasenfeld is the best:

| | |
|---|---|
| Sodium salicylate | 8.0 |
| Caffeine sod. salicylate | 2.0 |
| Water or saline | 50.0 |

Dissolve and filter.

The injections were begun in April, 1915, and continued to June, 1916, in four series of animals. In human cases, injections were begun several years ago, men being already reported.

INTRAVENOUS INJECTIONS. Second series: In testing the effects and comparative lethal doses of synthetic and natural sodium salicylate, 8 rabbits, averaging 3½ pounds each, were used—4 for the synthetic and 4 for the natural salts.

Intravenous injections were given, using the marginal ear veins, beginning with 200 mg. and increasing 100 mg. at a time until 800 mg. was reached.

Practically no symptoms developed from either the synthetic or natural salts, and it was impossible to see any difference between the two salts. Rabbits injected with 800 mg. of either the synthetic or natural salts died almost immediately after receiving the injection.

These injections were given twenty-four hours apart to permit the rabbits to eliminate the salts and to recover from the shock of the previous injections.

The only obvious symptoms of these injections short of the lethal dose was a rapid necrosis of the ears of the rabbits injected.

CONCLUSION. There is, in rabbits, no very obvious difference in the toxic action between synthetic and natural sodium salicylate when injected intravenously.

SUBCUTANEOUS INJECTIONS. Subcutaneous injections of synthetic and natural sodium salicylate failed to show any difference in toxicity. As these injections were very painful to the rabbits they were not carried beyond 800 mg., which was not lethal, and in fact produced no symptoms excepting those of extreme pain at the sight of injections, which subsided in from five to ten minutes.

*Administered through Stomach Tube.* The rabbits averaging 3½ pounds in weight were given respectively 1.5 gms. of natural and synthetic sodium salicylate dissolved in distilled water, administered through stomach tube, the stomachs of both animals being empty. The only symptoms of the above amounts were that rabbits were very quiet for an hour and a half, after which period they ate carrots with normal relish. At frequent intervals the animals were made to move about their cages, but no signs of paralysis were observed.

This treatment was continued at twenty-four-hour intervals, increasing each dose by 1.5 gm. (without any symptoms with the exception that the rabbits waited, before eating, for longer and

longer periods of time after treatment). Following the introduction of 6 gms. of the natural and synthetic salts, both rabbits showed symptoms of distress, and shortly became paralyzed. The rabbit that had been given the synthetic salt showed constantly increasing severity of symptoms, and finally became completely paralyzed, and died seven hours after receiving 6 gms. of the synthetic salt.

The rabbit that received the 6 gms. of the natural salt showed immediate symptoms of distress and became partially paralyzed, but those symptoms gradually subsided, and the following morning the animal ate carrots and bread without difficulty, and with seeming relish. This rabbit lived about two weeks and seemed to be normal in every way, but it died suddenly just after eating carrots. Autopsy failed to show any stomach lesions, but the liver showed extensive coccidiosis infection.

The synthetic rabbit, on autopsy, showed an inflamed stomach distended with fecal matter; other organs seemed to be macroscopically normal.

*Second Pair of Rabbits Given Salts by Stomach.* The above test was repeated with two rabbits weighing 4 pounds each. One rabbit received 5 gms. of natural sodium salicylate and the other one received 5 gms. of synthetic sodium salicylate, dissolved in 10 c.c. of distilled water and made up to 40 c.c. when administered by stomach tube. Both showed slight signs of distress in a few moments, but soon settled down quietly in their cages, neither showing any inclination to eat or drink. The natural rabbit died in three and a half hours without having developed any marked symptoms or signs of paralysis.

The rabbit that received the synthetic salt died some time during the night, but at the time of the death of the rabbit that received the natural salt the rabbit that had received the synthetic salt, while he would not eat, seemed in very good condition.

Postmortems of both of the above animals showed badly inflamed stomachs that were very much distended and filled with fecal matter.

*Third Pair of Rabbits Given Salts by Stomach.* These rabbits weighed $3\frac{1}{4}$ and 4 pounds. The $3\frac{1}{4}$-pound rabbit was given 4 gms. of the natural salt and the 4-pound rabbit was given 4 gms. of the synthetic salt. Both animals, like previous ones, became very quiet in a few moments and refused to move about their cages unless forced to, neither, however, showing any signs of paralysis.

In three hours and a half after ingesting the salt the natural rabbit was suddenly seized with a convulsion and died in a few moments. Postmortem showed a badly inflamed stomach distended with fecal matter.

The synthetic rabbit, however, drank freely of water and ate a carrot about four hours after ingesting the salt, and is still alive and eats well, but shows marked disinclination to move about.

CHART I.

| | Doses given intravenously. | Date. | Temperature at time of injection. | Time of injection. | Temperature readings at five-minute intervals after injection. | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 5 min. | 10 min. | 15 min. | 20 min. | 25 min. | 30 min. | 35 min. | 40 min. | 45 min. | 50 min. |
| | | 1915 | | | | | | | | | | | | |
| Natural salt | 200 mg. | June 17 | 37.0° C. | 2.40 P.M. | 37.4° C. | 38.0° C. | 38.0° C. | 36.0° C. | 35.0° C. | 36.0° C. | 37.0° C. | 37° C. | 37° C. | |
| Synthetic salt | 200 mg. | June 19 | 37.0° C. | 10.45 A.M. | 38.0° C. | 38.0° C. | 38.0° C. | 37.5° C. | 37.0° C. | 37.0° C. | 36.8° C. | 37° C. | 37° C. | 37° C. |
| Synthetic salt | 200 mg. | June 22 | 36.8° C. | 5.45 P.M. | 36.6° C. | 37.4° C. | 38.0° C. | 37.4° C. | 37.0° C. | 37.0° C. | 37.0° C. | 37° C. | 37° C. | 37° C. |
| Natural salt | 200 mg. | June 24 | 37.2° C. | 11.40 A.M. | 38.2° C. | 38.0° C. | 37.8° C. | 37.8° C. | 37.5° C. | 37.2° C. | 37.0° C. | 37° C. | 37° C. | 37° C. |

Weight of rabbits, 2¾ pounds; same rabbit for both tests.

CHART II.

| | Doses given intravenously. | Date. | Temperature at time of injection. | Time of injection. | Temperature readings at five-minute intervals after injection. | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 5 min. | 10 min. | 15 min. | 20 min. | 25 min. | 30 min. | 35 min. | 40 min. | 45 min. | 50 min. |
| | | 1916 | | | | | | | | | | | | |
| Natural salt | 200 mg. | June 17 | 37° C. | 2.40 P.M. | 37.4° C. | 38° C. | 38° C. | 36.0° C. | 35° C. | 36° C. | 37.0° C. | 37° C. | 37° C. | |
| Synthetic salt | 200 mg. | June 19 | 37° C. | 10.45 | 38.0° C. | 38° C. | 38° C. | 37.5° C. | 37° C. | 37° C. | 36.8° C. | 37° C. | 37° C. | 37° C. |

*Conclusion.* There is apparently no difference in the toxic and and irritant properties of synthetic and natural sodium salicylate in large doses. What the effects of the therapeutic doses administered to rabbits over a considerable period of time are is a question that can only be answered by a series of long and careful experiments, which we are now undertaking.

In experimenting with large doses the individual equation of the animal seems to count for more than the weight of the animal or the amount of the drug administered.

TEMPERATURE EXPERIMENTS. Here, again, rabbits differ from dogs in their behavior to the salicylates. Whereas dogs showed no drop in temperature, the curve in rabbits was irregular, from which it is difficult to deduce a rule.

SUBSEQUENT EXPERIMENTS—SUMMARY.

NATURAL SODIUM SALICYLATE.

| Rabbit. | Date. | Injected, mg. | Symptoms. | Weight of rabbit approximately three pounds. |
|---|---|---|---|---|
| No. 1. | Oct. 9, 1915 | 200 | 4.30 P.M. | No symptoms. |
| | Oct. 14, 1915 | 300 | 3.25 P.M. | " " |
| | Oct. 15, 1915 | 400 | 4.25 P.M. | " " |
| | Oct. 15, 1915 | 500 | 11.10 A.M. | " " |
| | Oct. 15, 1915 | 600 | 4.30 P.M. | " " |
| | Oct. 16, 1915 | 700 | 11.20 A.M. | Slight symptoms of shock, with rapid recovery. |
| No. 2. | Oct. 15, 1915 | 600 | 2.30 P.M. | No symptoms. |
| 2. | Oct. 15, 1915 | 700 | 4.00 P.M. | Slight symptoms of shock with rapid rerecovery. |
| 3. | Oct. 18, 1915 | 800 | 4.55 P.M. | Died immediately after injection. |
| 4. | Oct. 18, 1915 | 800 | 5.10 P.M. | Died immediately after injection. |
| 5. | Oct. 18, 1915 | 400 | 5.20 P.M. | No symptoms. |
| 5. | Oct. 20, 1915 | 600 | 10.40 A.M. | Incoördination for a few minutes; rapid recovery. |

SYNTHETIC SODIUM SALICYLATE.

| | | | | |
|---|---|---|---|---|
| No. 1. | Oct. 9, 1915 | 200 | 4.20 P.M. | No symptoms. |
| 1. | Oct. 14, 1915 | 300 | 3.20 P.M. | " " |
| 1. | Oct. 14, 1915 | 400 | 4.30 P.M. | " " |
| 1. | Oct. 15, 1915 | 500 | 11.15 A.M. | " " |
| No. 2. | Oct. 15, 1915 | 400 | 2.35 P.M. | No symptoms. |
| 2. | Oct. 15, 1915 | 500 | 3.30 P.M. | " " |
| 2. | Oct. 16, 1915 | 600 | 4.20 P.M. | " " |
| 2. | Oct. 17, 1915 | 700 | 11.15 A.M. | " " |
| No. 3. | Oct. 16, 1915 | 800 | 2.45 P.M. | Died immediately after injection. |
| No. 4. | Oct. 16, 1915 | 800 | 3.00 P.M. | Died immediately after injection. |

EXPERIMENTS IN DOGS.—Vinci has reported the results of experiments in dogs. He administered sodium salicylate subcutaneously in a few instances intravenously and by the stomach tube. He

noted collapse, with fairly quick recovery, attempts to vomit, and salivation. He used the synthetic acid of Bayer.

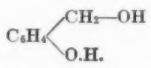
Collapse and salivation were the chief symptoms in our experiments with doses of 4 gms. in a dog weighing 8 kgs. The animal recovered. During convalescence there was weakness, also a dragging of the hind legs. The temperature did not fall.

*Experiment, Fourth Series. September,* 1915. Black, short-haired mongrel, 8 kgs.; 11 A.M., subcutaneous injection of 4 gms. natural sodium salicylate in 20 c.c. saline solution. Injection very painful. Salivation: dragging of legs. Recovery. The motions of the dog were at first excited, then stupid, then like collapse.

*Toxic Doses.* There is virtually no difference between the natural and synthetic acids except a difference arising from the less irritant action of the former. It is better borne by the stomach, and this fact slightly affects the toxicity in human beings. In rabbits the fatal dose was found to be 900 mg. to the kilogram of body weight. Toxic effects in dogs were noted after 0.5 gm. to the kilogram. Fatal doses were not tried. According to Vinci the fatal dose in dogs is 0.2 to 0.5 gm. to the kilogram of body weight.

*Fatal Cases.* We have been unable to find the report of any case fatal after the natural acid. Most of the deaths recorded were caused by sodium salicylate, and presumably the commercial product.

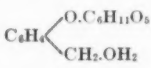
*Comparative Clinical Effects.* To make sure of obtaining a natural product through chemical changes in the living organism it is well to prescribe salicin. This glucoside is hydrolyzed in the organism, with the ultimate formation of salicylic acid, *e. g.:*



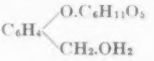

Salicin compares favorably with the synthetic salicylates. It has less action on the stomach and digestion. It was administered in 30 cases at the University and Bellevue Hospital Medical College and the Vanderbilt Clinic. The 5-grain tablets in use at these clinics are too small a dose. Twenty grains every four hours is the most satisfactory, but in these doses, as Dixneuf has pointed out, salicin must be carefully employed.

*Acute Rheumatism.* Saligenin, or salicyl alcohol, was used in 6 cases. Thirty grains were given three times a day. It is more powerful than salicin, is more effective, and in these doses produced noises in the ears and some salivation. It must be used with care.

The reason for the powerful effects of saligenin may be that it has a phenol and an alcohol group arranged thus:



Salicin, which is less active, is a monoglucoside, a natural product of saligenin, in which glucose is substituted for the phenol nucleus, *e. g.:*



*Phthalic Acid.* It is stated by Juvalta that phthalic acid is oxidized into salicylic acid and phenol. Mosso, however, was unable to confirm this result. He apparently leaves it undetermined after experiments which he says are insufficient. Stockman has recently spoken of phthalic acid as mediocre in its effects.

Phthalic acid as cotarnine phthalate was used in 3 cases of acute rheumatism. Its action on pain is very satisfactory. Phthalic acid is decomposed completely in the human organism:

Sodium cinnamate was used in 60 cases by subcutaneous injection. The injections are very painful unless controlled by anodynes. It is effective if it can be given in large enough doses, but owing to its relatively slight solubility it is not easy to employ more than 1 gm. at a time.

Methyl salicylate, used locally, has an excellent, if passing, effect on the pain and swelling of acute rheumatism.

Factors in Cases of Poisoning. It was clearly shown by Mlle. Chopin, in her thesis, that sodium salicylate is more quickly excreted in children than in adults and more quickly in healthy adults than in nephritics. The inference is fairly obvious. Salicylic acid or sodium salicylate tends to be more toxic when the kidney is impaired. Other causes affecting toxicity, as we have noticed, are: (1) Alcoholism; in these cases the salicylates should be given with caution. (2) The state of the stomach. (3) Diseases of the alimentary tract affecting the oxidizing of the benzol nucleus all increase the toxic effect of the salicylates. (4) Salivary glands. Salivation is always the symptom that precedes collapse, though delirium may occur first. Flushing of the skin is an early symptom of poisoning, especially worth notice, if nose-bleed occurs, too. Deafness and noises in the ears are very early symptoms. Disorders of the sense color, in which things look greenish or greenish yellow, as patients describe their perceptions, are late signs often noted during convalescence. The musical sounds, wholly abnormal and very disquieting, are intermediate between the period of rising cerebral disorder and dangerous collapse.

An experience of several years shows that these symptoms are almost equally incidental to both acids when pure, though they occur less frequently after the acid prepared from oil of birch or

gaultheria. In this respect the opinions of Latham and of Stokvis hold good today.

Fatal cases are recorded by different authorities. Vinci describes one after 35 gms. of sodium salicylate, the largest dose ever taken at a time. Headache, delirium, salivation, and coma, ending in death, marked the course of poisoning, as they do in others. In nearly all instances a cumulative effect, first noticed by Dixneuf, is reported. Such cases are not infrequent; instances are described by Sée, Chopin, Georges Huber, Wattelet, Quincke, Petersen, Empis, Heffermann, Binz, Koelin, Leonhardi-Aster, Fürbringer, von Jaksch, Wittich, Bertagnini, and Buss.

CONCLUSIONS. 1. When pure samples, whether natural or synthetic, are used the effects in animals are virtually the same.

2. The difference between the natural and synthetic salicylates in men is somewhat more distinct. In the case of the natural acid when administered to adults there was less gastric disturbance, the cerebral effects were slighter, and in general it may be said that this substance is better borne than the commercial acid.

3. It is not so toxic in very large doses, though when more than 75 grains are given in twenty-four hours there is a tendency to delirium in the susceptible to salivation and flushing of the integument.

4. The noises in the ears are noticed on the second day, as a rule, of administration.

5. It seems clear that the natural acid has less cumulative effect.

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# REVIEWS

A Manual of Physical Diagnosis. By Austin Flint, M.D., LL.D., Late Professor of the Principles and Practice of Medicine and of Clinical Medicine in Bellevue Hospital Medical College. Seventh edition, revised by Henry C. Thacher, M.S., M.D., Associate in Medicine in the College of Physicians and Surgeons of Columbia University; Assistant Attending Physician, Roosevelt and Lincoln Hospitals, New York. Pp. 381; 20 illustrations. Philadelphia and New York: Lea & Febiger, 1917.

After an interval of five years the seventh edition of Austin Flint's well-known *Manual of Auscultation and Percussion* appears under the auspices of a new reviser. The first four editions, appearing between the years 1876 and 1885, were revised by the author; the fifth, revised by J. C. Wilson, appeared in 1890; the sixth by Haven Emerson in 1912. A comparison with the six previous editions reveals a steady but small growth both of the book and of the subject, which stands, however, in marked contrast to the enormous development of most medical subjects during the same period.

In a work of such historical interest it seems unfortunate that the title of the present edition had to be changed to that of a *Manual of Physical Diagnosis*, even though it was necessary to include pulse-tracings and other subjects that could not properly be included under the head of auscultation and percussion. The omission of an important chapter on the physical examination of the nervous system, which had been introduced into the fifth edition, is also to be regretted. The space thus gained has been devoted to an opening chapter on the physics of sound. The other two extra chapters of the fifth edition (on the abdomen and on the order of physical examination) have been retained.

The general form of the early editions, which so clearly and accurately present the essentials of a large subject in a small space, has been adequately maintained. E. B. K.

The Early Diagnosis of Tubercle. By Clive Riviere.

The subject with which this small hand-book deals is of the greatest importance to every practitioner of medicine, as upon it depends not only the cure of the patient but also the prevention

of a possible source of infection to other individuals. The book presents the subject in a very accessible form, which renders it convenient for reference, the reading matter being concise and to the point. This is especially true of that portion of the book dealing with the physical examination of the patient, in which the various steps are well arranged and contain many points in the examination which, although they may appear trivial, are of the utmost importance in the carrying out of a careful examination in a doubtful case. It is to be regretted that the effort to be brief and concise has led the author to abbreviate this most important section of the book.

Undue prominence is given the sections on tuberculin and the use of the roentgen-rays, which are usually not available in the average patient. The chapters on sputum and temperature, while very good, would be improved if allotted some of the space devoted to the special tests above mentioned. The section on tuberculosis in childhood is mainly of value in calling attention to this condition and leading to a more thorough study of the chests of children in which tuberculosis is suspected. The value of the physical signs in the illustrative cases would be considerably increased if they were supported by autopsy findings instead of skiagrams.

Anyone interested in the careful examination of the chest will find in this small volume a great deal of valuable information, arranged in such a manner as to be readily accessible, very readable, and concise. F. A. C.

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PHARMACOLOGY AND THERAPEUTICS: FOR STUDENTS AND PRACTITIONERS OF MEDICINE. By HORATIO C. WOOD, JR., M.D., Professor of Pharmacology and Therapeutics in the University of Pennsylvania; Second Vice-Chairman of the Committee of Revision of the U. S. Pharmacopœia. Second edition. Pp. 455; 28 illustrations. Philadelphia and London: J. B. Lippincott Company.

THE value of Dr. Wood's original edition of this work and numerous recent advances in pharmacology and therapeutics have demanded this revision. Its publication has been delayed sufficiently to bring it into complete conformity with the new *United States Pharmacopœia*. All the official drugs are included, although the author explains that some of them are of little value, and some unofficial drugs are recognized because of their practical importance. The substitution of "mil" for C.c. is made, but the metric doses are still parenthesized.

The first chapter includes definitions, weights and measures, prescription-writing, incompatibilities, etc., while the rest of the book is devoted to the drugs. These are arranged in groups accord-

ing to their effects: for instance, those affecting secretion are taken up together, likewise those affecting the nervous system, the circulatory system, etc. In each instance they are first discussed briefly as a group, and then each drug is considered in regard to its materia medica, physiological action, and therapeutic uses. At the close of the discussion of the drugs in each group are given references to the literature, this feature adding greatly to the value of the text-book.

On the whole this book seems to the reviewer concise and yet sufficiently elaborate for students and practitioners, somewhat dogmatic and yet eminently practical in its presentation of only the important facts in relation to drugs. T. G. M.

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THE ANIMAL PARASITES OF MAN. By H. B. FANTHAM, M.A., Lecturer on Parasitology, Liverpool School of Tropical Medicine; J. W. W. STEPHENS, Jones Professor of Tropical Medicine, Liverpool University, and F. V. THEOBALD, M.A., Professor of Agricultural Zoölogy, London University. Partially adapted from Braun's *Die Tierschen Parasiten des Menschen* (4 ed., 1908), with an appendix by Dr. OTTO SEIFFERT. Pp. 900; 423 illustrations. New York: William Wood & Co.

THE present volume is a translation and elaboration of Braun's standard work on parasites, but with such a vast amount of new matter and so many alterations that the identity of the German work has largely disappeared. The introduction remains much the same, with modifications according to the English authors. The new edition contains many references to general parasitism. Fantham has undertaken the classification of the protozoa, and has followed very closely after the original. He, however, uses the class name of Sarcodina of Bütschli in place of Rhizopoda, and traces the history of development of these organisms to some extent. The section of Flagellata, especially the Trypanosomes, has received very great elaboration, and the Leishmania are well described. Under Coccidiidea the authors have used the genus name of Eimeria of Schneider for Coccidia of Leuckart. The section on Hemasporidia has received considerable amplification, much attention being given to Theileria and Babesia. Chlamydozoa are treated generally at the end of the section on Protozoa, but one misses the Kurloff bodies, a structure upon which many original observations have been made. Platyhelminths have been treated by Dr. Stephens, who has lengthened the general description and adopted an almost entirely new classification largely based upon older writers, but also upon some work appearing since the German edition. His

of a possible source of infection to other individuals. The book presents the subject in a very accessible form, which renders it convenient for reference, the reading matter being concise and to the point. This is especially true of that portion of the book dealing with the physical examination of the patient, in which the various steps are well arranged and contain many points in the examination which, although they may appear trivial, are of the utmost importance in the carrying out of a careful examination in a doubtful case. It is to be regretted that the effort to be brief and concise has led the author to abbreviate this most important section of the book.

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THE ANIMAL PARASITES OF MAN. By H. B. FANTHAM, M.A., Lecturer on Parasitology, Liverpool School of Tropical Medicine; J. W. W. STEPHENS, Jones Professor of Tropical Medicine, Liverpool University, and F. V. THEOBALD, M.A., Professor of Agricultural Zoölogy, London University. Partially adapted from Braun's *Die Tierschen Parasiten des Menschen* (4 ed., 1908), with an appendix by Dr. OTTO SEIFFERT. Pp. 900; 423 illustrations. New York: William Wood & Co.

THE present volume is a translation and elaboration of Braun's standard work on parasites, but with such a vast amount of new matter and so many alterations that the identity of the German work has largely disappeared. The introduction remains much the same, with modifications according to the English authors. The new edition contains many references to general parasitism. Fantham has undertaken the classification of the protozoa, and has followed very closely after the original. He, however, uses the class name of Sarcodina of Bütschli in place of Rhizopoda, and traces the history of development of these organisms to some extent. The section of Flagellata, especially the Trypanosomes, has received very great elaboration, and the Leishmania are well described. Under Coccidiidea the authors have used the genus name of Eimeria of Schneider for Coccidia of Leuckart. The section on Hemasporidia has received considerable amplification, much attention being given to Theileria and Babesia. Chlamydozoa are treated generally at the end of the section on Protozoa, but one misses the Kurloff bodies, a structure upon which many original observations have been made. Platyhelminths have been treated by Dr. Stephens, who has lengthened the general description and adopted an almost entirely new classification largely based upon older writers, but also upon some work appearing since the German edition. His

treatment of the Nemathelminths has followed the same character. A few of the genus names have been changed.

Following this capital comes a short chapter on the observation, preservation, and cultivation of Platyhelminths and the Nematodes. This is followed as before by Acanthocephala and Hirudinea. Theobald has written the section on Arthropoda, and greatly enlarged it by including newer additions and putting in keys to the various families and genera. The flies and mosquitoes have received much attention. The next section, called addenda, cites some of the rarer parasitic manifestations, *e. g.*, myiasis, and means to combat them.

A supplement of over one hundred pages reviews concisely the pathogenic relations of the animal parasites, and gives specific treatment. The remainder of the book is given over to appendices on Protozoölogy, including recent researches, culture media and technic, and on Trematodes and Nematodes, in which a few unusual findings and results are discussed.

At the end of the text all the references are collected according to subjects, with a guide to the page or pages on which each is discussed, and the names are arranged alphabetically. In former editions these lists were given after each subject, in many ways a preferable arrangement. The index is very full and satisfactory. Many illustrations have been added and the old ones much improved in reproduction. The book is a splendid systematic reference work and as well a text-book of pathogenic parasitology.

H. F.

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A Text-book on the Practice of Gynecology. For Practitioners and Students. By W. Easterly Ashton, M.D., LL.D., Professor of Gynecology in the Graduate School of Medicine of the University of Pennsylvania. Sixth edition, thoroughly revised. Pp. 1097; 1052 drawings. Philadelphia and London: W. B. Saunders Company.

The sixth edition of this book upholds the prestige that has been gained by the former editions, and contains much additional matter. Several of the chapters have been extensively revised, with a resulting improvement in the book as a whole. The great value of this work lies in the fact that the author takes nothing for granted on the part of the reader's knowledge, and minutely describes the smallest details, to the end that even the novice must understand the technic and rationale of the various gynecological measures advised. Viewed from a critical stand-point, however, the failure to even mention radium is a noticeable omission in a chapter on cancer of the uterus that is otherwise excellent, and a brief description of adenomyoma would not be out of place. Likewise, the

usefulness of pyelography might be mentioned in considering diseases of the kidneys. The book is rapidly assuming huge proportions, giving evidence of the advances which have been constantly made in this field, and unless some of the subject matter is curtailed it is probable that future editions may be in two volumes.

To the student and general practitioner this work will undoubtedly continue to be a valuable aid, but, on the other hand, there is nothing unusual about the book that is of particular interest to the specialist. F. E. K.

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CARE OF PATIENTS UNDERGOING GYNECOLOGICAL AND ABDOMINAL PROCEDURES BEFORE, DURING AND AFTER OPERATION. By E. E. MONTGOMERY, A.M., M.D., LL.D., F.A.C.S., Professor of Gynecology in Jefferson Medical College; Gynecologist to Jefferson and St. Joseph's Hospitals; Consulting Surgeon to the Philadelphia Lying-in Hospital, the Jewish Hospital, the Kensington Hospital for Women, and the American Oncologic Hospital. Pp. 144; 61 illustrations. Philadelphia and London: W. B. Saunders Company.

THIS interesting monograph, detailing the practice of the author, supplements the usual teaching of pelvic surgery to the medical student or nurse. To the often perplexed intern or nurse fresh on a surgical service it answers the question of how to do this or that minor procedure necessary to the comfort and well-being of the patient. The operating-room assistant or nurse may profit from a study of the illustrations if nothing else. The teaching is safe, well founded, and eminently practical. P. F. W.

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DISEASES OF INFANCY AND CHILDHOOD. By L. EMMETT HOLT, M.D., Sc.D., LL.D., Professor of Diseases of Children in the College of Physicians and Surgeons (Columbia University), New York, and JOHN HOWLAND, A.M., M.D., Professor of Pediatrics in the Johns Hopkins University, Baltimore. Seventh edition. Pp. 1180; 215 illustrations. New York and London: D. Appleton & Co.

IN the seventh edition of this standard work the excellence of the former editions is continued and the book is made more valuable by complete revision in many places, bringing all the chapters up to date.

In Part I are found the instructive chapters on hygiene, and care, growth and development and peculiarities of disease in

children. In the latter chapter, as might be expected, stress is laid upon the physical examination of babies and children. The section on nutrition has been considerably enlarged and changed, and embodies all the newer ideas of value in this rather extensive and rapidly advancing field. Especially full chapters are included on hereditary syphilis and influenza, and a separate chapter deals with epidemic catarrh or la grippe. The pathology of the diseases of the heart and kidneys, and especially of the intestine, is fully discussed and well illustrated.

The reviewer has been accustomed to consider Dr. Holt's book in the light of the "Bible of Pediatrics," and believes it to be as complete and thorough as a single volume text-book can be made. Indeed, it would seem that it should be in the library of every physician whose practice brings him into contact with children.

A. G. M.

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LOSSES OF LIFE IN MODERN WARS: AUSTRIA–HUNGARY AND FRANCE. By GASTON BODART, LL.D. MILITARY SELECTION AND RACE DETERIORATION. By VERNON LYMAN KELLOGG, Standford University. Edited by HARALD WESTERGAARD, LL.D., Member of the Committee of Research of the Division of Economics and History of the Carnegie Endowment for International Peace. Pp. 207. Oxford: At the Clarendon Press, Humphrey Milford.

ONE's favor is immediately elicited for this book, as well as for its companion upon *Epidemics Resulting from Wars*, on account of the handsome way in which it is constructed. The binding is blue cloth, the pages of the best paper, the type large and distinct, and the tables, of which there are many, in full-size type and never crowded. These features are especially noteworthy in view of the present tendency of some publishers to make use of cheap materials and to put the most possible on the individual page.

The first division of the work consists of two parts: the first dealing with the wars of Austria-Hungary between 1618 and 1913, and the second with those of France between 1614 and 1913. The available data upon the human losses of these wars are presented elaborately in tables, and the text on the basis of the tabulated figures makes out a case against war. Exception may be taken, however, to the conclusion drawn at the close of this division of the book that the present stagnant condition of France may be looked upon as a result of her preëminence as a war-like nation. The former premise is to be questioned in view of the part France is now playing in the European war.

In the final part of the work Kellogg presents a preliminary report and discussion upon the race-deteriorating influences of war. He makes three points: (1) that the men who are most fit mentally

and physically are the ones lost in war, the less fit being left for the reproduction of the race; (2) that the influence of the Napoleonic wars was to reduce the stature of the French male population and to increase their youthful infirmities and disease; (3) that venereal diseases are increased during war and that their effects are racially deteriorating. The facts submitted in substantiation of these conclusions are convincing and will be difficult to refute.

T. G. M.

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THE OBSTETRICAL QUIZ FOR NURSES. A MONOGRAPH ON OBSTETRICS FOR THE GRADUATE AND UNDER-GRADUATE NURSE IN THE LYING-IN ROOM. By HILDA ELIZABETH CARLSON. Pp. 305. New York: Rebman Company.

THE familiar plan of a quiz compend serves as a form for this excellent treatise on obstetrics for nurses. While the text is therefore necessarily shortened at times, the essential principles are presented with sufficient thoroughness to afford a clear description of the subject at hand. From the form of the book it should be of value in teaching obstetrics to nurses. The book is divided into twenty chapters which take up the various subjects of obstetrics. There are chapters on modifications of cows' milk, preparation of solutions and enemata and a brief description of the various measures used to alleviate the pains of labor. A careful study of the book will place a nurse in a state of preparedness to efficiently assist the physician and properly care for her patients. An essential feature is a description for improvising many things needed on an emergency or complicated case, outside of the maternity. The book is highly commended to nurses and teachers of nurses.

P. F. W.

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MANUAL OF SURGICAL ANATOMY. By LEWIS BEESLY, F.R.C.S., Lecturer on Surgery and Operative Surgery, Edinburgh School of Medicine, and Lecturer on Surgical Applied Anatomy, Edinburgh Postgraduate Courses, and T. B. JOHNSTON, Lecturer and Demonstrator of Anatomy, Edinburgh University, and Lecturer on Medical Applied Anatomy, Edinburgh Postgraduate Courses. Pp. 537; 164 illustrations. New York: William Wood & Co.

THE writer of a book on surgical anatomy attempts a difficult task in deciding how much attention he should give to the surgical and how much to the anatomical side of the subject, for the book that covers the whole range on both sides has not yet been written. The authors have presented an excellent combination of the two.

The particular purpose has been to encourage the study of surgical anatomy from dissections, which all recognize is the best way to study gross anatomy for any purpose. Only the undergraduate student, however, can avail himself of this method of study, as a rule. The anatomy of surgical operations has been emphasized, without including the details of surgical technic. Special attention is given to the relations which the ends of the diaphyses and the epiphyses bear to the capsules and synovial membranes of the adjacent joints. A fund of valuable information concerning the anatomical aspects of a large number of surgical conditions is compressed within the 537 small pages. The illustrations, especially the colored ones, are very good, and are well selected to show the value of a special knowledge of the anatomy of certain regions. Those showing sections of the joints are particularly instructive. A feature is also made of roentgen-ray illustrations. The whole book serves well the very useful purpose of proving the value of a practical knowledge of anatomy. T. T. T.

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DISORDERS OF THE SEXUAL FUNCTION IN THE MALE AND FEMALE. By MAX HÜHNER, M.D., Chief of Clinic, Genito-urinary Department, Mount Sinai Hospital Dispensary, New York City. Pp. 318; 4 illustrations. Philadelphia: F. A. Davis Company.

IN realization of the dearth of information by genito-urinary specialists on the sexual neuroses as manifested by their textbooks and personal admissions, the author has produced this short and practical treatise on the subject. Hühner, by virtue of his experience and technic in the treatment of the lower urological affections is far better qualified to present such a subject than the neurologist, upon whom in the past this responsibility has largely rested.

The author has refrained from entering upon the purely neurological aspects of the sexual disorders, except as a matter of elucidation; nor does he discuss psychanalysis or the various types of sexual perversions. These he refers to the neurologist as their pathology belongs to the domain of abnormal psychology. The author also chooses to disregard the venereal diseases in their connection with the subject under discussion. Sterility, likewise, is omitted since it has been accorded an independent treatise.

Thus the subject matter of the book comprises chapters devoted to masturbation, impotence, pollutions, priapism, satyriasis, nymphomania, dyspareunia, absence of orgasm in the female, enuresis, withdrawal, continence, etc.

The conciseness and practical manner of presentation recommends the work as an introduction to the subject of sexual neuroses.

B. A. T.

# PROGRESS
OF
# MEDICAL SCIENCE

## MEDICINE

UNDER THE CHARGE OF
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AND
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**The Inhibitory Action of Extract of the Posterior Lobe of the Hypophysis upon the Polyuria of Diabetes Insipidus.**—GEORGE EISNER (*Deutsch. Arch. f. klin. Med.*, 1916, cxx, 438) reports two cases of diabetes insipidus which came under his care, and in which he had the opportunity to study the effect of extracts of the posterior lobe of the hypophysis cerebri upon the polyuria. He first reviews the literature, showing that opposite effects were claimed by different groups of workers. Von der Velden, Romer, Farnu, Hoppe-Seyler and others claimed that they had shown both in man and in animals that extracts of the posterior lobe inhibited diuresis, not only in normal individuals but in patients suffering with diabetes insipidus, and that, these results being true, diabetes insipidus must be considered as a hypo-activity of the posterior lobe of the hypophysis. On the other hand, Frank and Steiger differed, having failed to demonstrate any diminution in urinary secretion following the injection of posterior lobe extract. They, therefore, stated that on clinical, pathological and anatomical grounds diabetes insipidus must be considered as a hyperfunction of the neurohypophysis. Eisner's first case was that of a soldier, aged thirty-five years, who, shortly following a fall upon his head in the summer of 1914 which rendered him unconscious for five minutes, developed headache and shortly after that a greatly increased thirst and a polyuria. In November, 1914, he contracted pneumonia; convalescing from this, he resumed his soldier's life, and in February, 1915, was admitted to the hospital suffering from an intestinal condition suspiciously like dysentery. During his convalescence from this illness he acquired an acute gonorrhea and on

June 4, 1915, he was transferred to Eisner's care. At this time the patient was consuming 15 to 17 liters of fluid daily and passing 15 to 17 liters of urine, the specific gravity of which was not over 1 or 1.001. The only objective finding of any importance on physical examination was an intraspinal pressure of 220 mm. of mercury with the patient in the lateral recumbent position. His mental condition was rather euphoric, and headache at times was so severe that he could not wear his cap. Experiments were tried in an attempt to differentiate the type of diabetes insipidus present in the case, as Meyer claims that there are two varieties: (1) True diabetes insipidus, in which the kidneys are unable to secrete a urine of normal concentration, and in which the addition of sodium chloride causes an increased flow of urine without an increased concentration, and (2) a so-called "psychopathic" diabetes insipidus in which the concentration of the urine is raised after the administration of sodium chloride. Therefore, after patient had been on a constant diet, various amounts of sodium chloride, urea, dextrose and lactose were administered, all of them producing an increase in the specific gravity, and concentration of the urine with very little, if any, increase in volume of output. The phenolsulphonephthalein output, when the dye was administered intravenously, was 83 per cent. during the first hour. After these determinations had been made, various extracts (hypophysin, pituglandol) of posterior lobe substance were administered intravenously, intramuscularly and by mouth. The administration of these extracts was constantly followed by a short period of lessened urinary secretion, the urine excreted during this time having a higher specific gravity and increased concentration of NaCl and urea. However, the daily output was not diminished. A second case came under Eisner's observation shortly after this one. This case was a woman, aged fifty-eight years, who had a breast amputated in March, 1915, for carcinoma, an affection in which diabetes insipidus has rather frequently been described. In August, 1915, she noticed an increased thirst and augmented urinary secretion, amounting to 4 to 6 liters daily. She developed a progressive exhaustion and sleeplessness, frequent morning vomiting, and dryness of the mouth. Strychnin was injected without result and in October, 1915, she came into the hands of the writer. At this time the patient was large, well nourished but weak, with evidence of slight arteriosclerosis. Chest was negative and liver was slightly enlarged and firm. The scar on breast was healed, with no palpable lymph glands. Roentgenograms of skull showed multiple nodules in the skull. The urine averaged 4 liters per day, with a specific gravity of 1.002 to 1.005. Her health did not improve during her six weeks' stay in the hospital, and she died a few weeks after her discharge. In this patient the administration of sodium chloride resulted in a slight increase in the daily output of urine, while the specific gravity remained the same. About two-thirds of the salt was excreted in the same day, and the remainder on the following day. The experiments with urea did not give any definite results. The administration of hypophysin, however, gave distinct results in the urinary output for the day being distinctly lower, with increased specific gravity and higher concentrations of sodium chloride and urea. Eisner concludes from these experiments that extracts of the posterior lobe of the hypophysis will

diminish urinary secretion and increase the concentration and specific gravity of the urine in this group of cases of diabetes insipidus (with changes in the central nervous system) but that the effect is only temporary, and therefore these extracts cannot be regarded as an effective remedy. The value of the posterior lobe extract in diabetes insipidus must be as a diagnostic measure, for, if injections of the extract diminish the urinary output, and produce a urine that is normal or nearly so, the group of cases in which this result is obtained must be regarded as arising from diminished functionating of the posterior lobe of the hypophysis.

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**An Improvement of the Phenolphthalin Test for the Occult Blood in the Feces.**—Boas (*Deutsch. med. Wchnschr.*, 1915, xli, 549) describes the modification of his recently proposed method of performing the phenolphthalin test for occult blood in the feces. The reagent is prepared as follows: 25 gms. of potassium hydrate are dissolved in 100 c.c. of distilled water, 1 gm. of phenolphthalin is added and the mixture is shaken vigorously. After solution is complete powdered metallic zinc is added and the preparation is boiled in an Erlenmeyer flask until the fluid is completely decolorized (two to three hours). After cooling, distilled water is added up to the original volume. Solution is filtered and the result is a water-clear solution, which remains colorless even after adding acetic acid, hydrogen peroxide and alcohol. The solution remains unchanged for several weeks. In the course of a few weeks oxidation of the phenolphthalin around the edge of the bottle may take place; this may color the first few drops of the solution pink and the bottle should therefore be wiped clean before using. The method of performing the test is as follows; an acetic acid-alcohol extract (5 drops of glacial acetic acid and 15 to 20 c.c. of alcohol) of the feces is prepared. From a dropping bottle 15 drops of the reagent are placed in a test-tube, to which are added 5 to 6 drops of 3 per cent. hydrogen peroxide and 2 c.c. of absolute alcohol. The tube is well shaken. The fecal extract is then run into the tube slowly so that it forms a layer. If blood coloring matter is present there appears either immediately or gradually a rose color or deep red ring at the line of contact. The depth of color depends on the amount of blood present. If the color is faint, it is more readily perceived by placing the tube before a white background. The result of the test is rarely doubtful but when such is the case the author proceeds in the manner devised by Schumm for increasing the delicacy of the guaiac test; the feces are rubbed with alcohol and ether in equal quantities in a crucible, filtered repeatedly and then the filtrate is evaporated to dryness. The dry residue is suspended in acetic acid-alcohol with the help of a stirring rod and filtered. Then the technic as described above is followed, when the ring becomes definite if blood is present. The author has compared the phenolphthalin test with the benzidin and guaiac tests and he has found the phenolphthalin test more delicate than the benzidin and much more sensitive than the guaiac. Whenever he has found the guaiac and benzidin tests positive the phenolphthalin test has been plainly positive. The observations described above relate only to the detection of blood in feces. For the detection of blood in the gastric contents this technic is not satisfactory as the author will show in a subsequent communication.

# SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

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**Traumatic Aneurysm Dealt with by Obliterative Arteriorrhaphy.**—JEFFERSON (*British Med. Jour.*, December 9, 1916, p. 794) reports a war case of true traumatic aneurysm in the left antecubital fossa, following a wound by a rifle bullet which gave little hemorrhage and healed within a few days. Two weeks after admission a pulsating swelling appeared and at the end of another four weeks it was the size of a hen's egg and was still increasing. A tourniquet having been applied to the arm the sac was laid open and the contained clots turned out. Three openings into it were discovered; one was small, situated on the inner aspect of the sac, and leading upward and backward. This was, probably, a common trunk of origin of the anterior and posterior ulnar recurrent arteries. Two larger openings in the lowest part of the sac were distant about ¾ inch from one another, and connected together by a deep groove. From them a probe passed upward and downward along the tracks of the brachial and ulnar arteries respectively. A probe sharply bent could be passed into the upper opening and then immediately downward along the course of the radial artery. Thus the condition was an aneurysm of the highest part of the ulnar artery. The interior of the sac was well scrubbed with iodine to promote adhesions, a continuous suture of fine chromic catgut on a fully curved intestinal needle was taken, and the smallest opening closed with four points of suture. In a like manner the upper opening was closed and the suture continued along the groove to close the lower opening. Following the recommendation of Matas, the sutures were made to enter the sac wall rather wide of the margins of the sides of the grooves. In this way was produced a firm approximation of as large a marginal surface as possible. The tourniquet was now removed and complete hemostasis seemed to have been secured. A second row of sutures was now inserted about half way up the walls of the sac. The skin flaps had not been dissected at all from the subcutaneous surface of the sac and so were lined with smooth sac wall. Two relaxation sutures were then introduced on each side to complete the obliteration and silkworm gut sutures brought the skin edges into apposition. Recovery was uneventful and the result quite satisfactory.

**Comminuted Fracture of the Humerus Produced by Muscular Action.**—MUMMERY and GIUSEPPI (*British Med. Jour.*, December 9, 1916, p. 795) reports the case of a soldier, aged thirty-three years, who sustained a comminuted fracture while throwing an empty hand grenade, in practice, which was about the size of a duck egg, made of steel, and weighed just over two pounds. He had raised the grenade up to and

behind his shoulder, as in the first position for "chucking it," as one would do in throwing a stone, and he did this suddenly and with a jerk. He felt his arm break, and it and the grenade, which had not yet left his hand, dropped. The officer in charge and several other men, saw the accident happen, and there is no question as to this having been the exact method of its occurrence. The patient was an exceedingly muscular man, with thirteen years' service, who had never had any serious illness nor previously broken a bone. The roentgen-ray, operation, and a postmortem, a month and a half after the operation, showed the comminuted fracture.

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**Flavine and Brilliant Green.**—BROWNING, GULBRANSEN, KENNAWAY, and THORNTON (*British Med. Jour.*, January 20, 1917, p. 73), working in the Bland-Sutton Institute of Pathology, the Middlesex Hospital, say that they have, in the course of the past year and a half, examined an extensive series of substances, comprising the principal antiseptics in common use and also other compounds, some of which have not hitherto been recognized as antiseptics or applied as such. A substance belonging to the acridine group, flavine, has been found to possess extremely powerful bactericidal and antiseptic properties, which are enhanced rather than diminished by admixture with serum. In this respect flavine differs from all the powerful antiseptics in common use. In the presence of serum, flavine is the most powerful bactericide of all those investigated for both Staphylococcus and B. coli, and it is equally efficient for the enterococcus and for anaërobes such as B. edematous maligni. Flavine, in relation to its bactericidal power, is very much less detrimental to the process of phagocytosis and less harmful to the tissues than the other substances; hence much higher effective concentrations can be employed without damaging the tissues or interfering with the natural defensive mechanisms. Brilliant green also compares most favorably with the other antiseptics in these respects. Clinical results have substantiated the estimate of the therapeutic value of flavine and brilliant green based on the characters above noted. The duration of septic conditions is in general reduced to at least a half, the stimulus to connective tissue to form granulations is a very outstanding feature, and these antiseptics can be applied in considerable amounts with the minimum of interference with the normal tissue functions. As regards the comparative merits of brilliant green and flavine, the latter is considered both the more efficient and the more rapid in action.

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**Flavine and Brilliant Green in the Treatment of Infected Wounds.**—LIGAT (*British Med. Jour.*, January 20, 1917, p. 78) says that for over a year he has employed flavine compounds and brilliant green in septic cases under his care in the Middlesex Hospital. Upward of 150 cases have been treated, about 50 per cent. of these being war wounds. In the case of suppurating wounds the procedure followed has been to secure adequate drainage by free incision when necessary, and then to irrigate with a 1 to 1000 solution of the antiseptic in normal saline, finally the wound is covered with gauze soaked in the solution, and protective applied to prevent evaporation. Where there has been a cavity it has been packed lightly with gauze soaked in the solution. A considerable diminution of the discharge of the pus may be expected

at the end of twenty-four hours. In wounds of moderate severity in which no foreign body is present and in which free drainage is secured, the suppurative process may be expected to come to an end after four or five days' treatment. From the few cases in which there has been an opportunity to apply the antiseptic before the evidence of sepsis has appeared it is considered that the results of the highest value are to be anticipated in the future by what one may term the "prophylactic" use of these antiseptics. Ligat has used considerable quantities both of brilliant green and flavine over prolonged periods; in some cases he has no hesitation in injecting the latter antiseptic into the tissues, and he has never observed any toxic phenomena following their use. Of the two antiseptics investigated he has found flavine to be the more efficient, especially in heavily infected wounds with free discharge of pus, and he now uses this antiseptic exclusively for septic cases. He regards these substances as satisfying therapeutic requirements for the treatment of wounds in a manner superior to any of the antiseptics hitherto employed.

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**The Bacteriology and Microscopy of the Contents of the Seminal Vesicles Postmortem. A Study of Fifty-two Cases.**—THOMAS and HARRISON (*Jour. Urol.*, 1917, i, 50) say that in view of the unprecedented interest manifested by urologists today in spermatocystitis, and in realization of the focal sepsis occasioned thereby, too little suspected and investigated by the average medical man, but nevertheless characterized by a retinue of urinary, arthritic, neurological, mental and even systemic diseases, it behooves the profession to welcome any attempt to study this obscure affection. Some investigators regard spermatocystitis as the commonest complication of gonorrhea. It is probably true that epididymitis does not exist without an associated seminal vesiculitis, and the belief is gradually gaining credence that inflammation of the spermatic vesicles is as common, if not more frequent than prostatitis, as a gonorrheal complication. Mayer found 60 per cent. of patients with posterior urethritis to have involvement of the seminal vesicles. Lewin and Bohm encountered spermatocystitis in 35 per cent., and prostatitis in 29 per cent. of 1000 gonorrheal cases. The particular purpose of the writers is to establish on a firmer basis certain indefinite and conflicting ideas concerning: (1) the presence of spermatazoa in the seminal vesicle, (*a*) normally and (*b*) when inflamed; (2) the life or death of spermatazoa in spermatocystitis and (3), the indentification of the invading bacteria, gonorrheal and non-gonorrheal. They concluded that the seminal vesicles harbor spermatozoa after death, and therefore presumably during life. This function is exercised in the presence of inflammation (spermatocystitis), although in a large percentage of inflammatory cases no spermatozoa can be found (postmortem). The determination of the viability of the zoösperm in the presence of the seminal vesiculitis, the exact identification, classification and relative frequency of the invading bacteria, particularly with reference to gonorrhea are questions impossible of solution by postmortem investigation.

# THERAPEUTICS

UNDER THE CHARGE OF

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**The Nature of Pneumonia and the Serum Treatment.**—COLE (*New York Med. Jour.*, 1917, cv, 233) from a study of pneumonia at the Rockefeller Institute, reports that most cases of pneumonia are caused by pneumococci which can be divided into at least four types. Over 500 cases of pneumonia have been studied for the purpose of determining the relative frequency of the different types of infection. The results showed that 60 to 65 per cent. of all cases were due to pneumococci of Types I and II, while 10 to 15 per cent. were due to pneumococci of Type III, the remaining 25 per cent. being due to pneumococci belonging to Type IV. Studies were also made to determine the frequency of occurrence of the different types in mouths of normal persons. In examinations of 527 people, 254, or about half, showed pneumococci. They belonged to the Type IV group in 75 per cent. In 17 per cent. the pneumococci were of the Type III group, while in less than 12 per cent. they were of the so-called fixed Types I and II. In practically all the instances in which organisms of Types I and II were found in normal mouths, it was possible to trace a close relationship between these individuals and a case of pneumonia of the same type. Pneumococci of Types I and II tend to disappear from the mouth in a short time as after convalescence from pneumonia. The author believes that isolation of cases of pneumococci of Types I and II should be more strictly observed than is the usual practice. With the present knowledge it was not possible to have an opinion on the value of isolation of cases due to pneumococci of Type III. Probably no effect would be obtained by isolation in cases of infection with Type IV. With regard to specific treatment the author believes that vaccine treatment is without much beneficial effect. He has made use of serum prepared from animals made immune to organisms of the different types. He notes that on account of the specificity of types it is necessary to determine the type of infecting organism in each case before instituting serum therapy. This determination of type of organism is of important prognostic value. The author has used immune horse serum prepared against the three important Types I, II, and III. The serum against pneumococci of Type I was of high power, that of Type II was considerably less powerful while that of Type III had very little effect, either in the test-tube or on experimental animals. So far no attempts have been made to use the serum on patients with Type III infection. A limited trial has been made with serum against pneumococci of Type II, but the results have not been promising. The use of immune serum against infection with organisms of Type I, however, has given very gratifying results and experience indicated that with proper

use this serum had great therapeutic value. In the hospital of the Rockefeller Institute, 78 cases were treated with 6 deaths. The mortality was 25 per cent. in cases due to Type I infection, before the serum was used, so that it was evident that the serum was of considerable value. Of the 6 fatal cases, 1 died on the fifty-third day following pneumonia from general streptococcus infection; 1 died during convalescence from pulmonary embolism; 3 were treated only on the day of death late in the disease, leaving but 1 fatal case that received treatment over two days. In order to obtain the best results certain rules must be observed. First, serum must be given in large amounts intravenously, and its administration must be commenced as early in the disease as possible; its use must be continued until infection was definitely overcome. Before administering the serum a small dose of normal horse serum should be given subcutaneously in order to desensitize the patient in case he was sensitive to horse serum. Among the treated cases the evidence of empyema has been greater than in the untreated cases. This probably meant that in a large number of the cases, otherwise fatal, the infection was localized instead of becoming general.

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**A Report on the Treatment of Pernicious Anemia by Transfusion and Splenectomy.**—GIFFIN (*Jour. Am. Med. Assn.*, 1917, lxviii, 429) says that there is no evidence that splenectomy has cured pernicious anemia. A review of 31 cases of splenectomy for pernicious anemia demonstrates a definite gain in the blood, the weight, and the general condition during the first three months of the postoperative period in 78 per cent. of the cases; during the second three months' period, 68 per cent. of living patients maintained their gain. A consideration of the advisability of splenectomy would seem to be warranted at present chiefly in young and middle-aged patients of good general resistance, who show evidence of active hemolysis and in whom the spleen is moderately enlarged. The estimation of the blood-derived pigments in the duodenal contents is valuable in determining the degree of hemolytic activity present at a given time. A comparison of the degree of hemolysis with the severity of the anemia would seem to be indicative of the productive power of the bone-marrow. Preoperative treatment, especially transfusions, should be employed to influence the general condition of the patients and to improve the characteristics of the blood picture. The operative risk is increased when the hemoglobin is below 35 per cent. and the erythrocyte count less than 1,500,000 cells. Postoperative transfusions have not been given as a routine procedure, but transfusions have been successfully employed in postoperative relapse.

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**The Treatment of Tuberculous Pericarditis by the Induction of an Artificial Pneumopericardium.**—WEIL and LOISCLEUR (*La Presse Méd.*, 1916, xxiv, 601) recommend the introduction of air into the pericardial sac after paracentesis of a pericardial effusion by employing a similar technic as in treating a pleurisy with effusion by artificial pneumothorax. They cite a case treated in this way with the treatment controlled by frequent roentgen-ray examinations. They believe that adhesion of the pericardial layers can be prevented

by this procedure, and preëxisting adhesions are generally broken up by the introduction of the air. The pericardial sac in the case treated by the authors continued to refill but the intervals between tappings became progressively lengthened from eight to fifteen to thirty-three to forty-eight days. The injection of air in an amount equal to that of the fluid removed caused no untoward effects; no pain, no dyspnea, no symptoms referable to the heart itself were produced.

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**Home-made Bread Substitutes for Diabetic Patients.**—NICHOLSON (*British Med. Jour.*, 1917, 2925, 82) recommends a bread made of peanut flour and casein. It has the advantage of being very nice to the taste, and can be cut readily into slices, even as thin as white bread. The formula for making it is as follows: Peanut flour, 8 ounces; casein, 2 ounces; a pinch of salt; white of eggs, 12 ounces. The white of egg is beaten to a snow, and then the other ingredients (previously lightly mixed) are slowly added.

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**Disappearance of Malignant Tertian Crescents from the Blood following the Intravenous Injection of Tartar Emetic.**—ROGERS (*British Med. Jour.*, 1917, 2923, 6) who has already reported success in the cure of kala-azar by tartar emetic intravenously, tried the same drug in the treatment of patients with persistent malarial crescents in the blood. He says that it is well known that once crescents appear in the blood they remain present for months uninfluenced by quinin, and cites the details of 4 cases treated by intravenous injections of tartar emetic with rapid disappearance of the crescents from the circulating blood. The author is not too sanguine but suggests the more wide-spread use to determine its value. He says that much further experience will be required to settle these points but the indications to be derived from these few cases appear to be that quinin should be used to check the malarial paroxysms, while tartar emetic should subsequently be given intravenously, in the hope that it may prove of value in destroying the extracorpuscular stages of the malarial parasites and so prevent relapses and greatly lessen the infectiveness of the patient to malaria-bearing mosquitoes by killing the crescents of the malignant tertian variety and the corresponding resisting forms of the other types of malaria.

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**Home-made Bread Substitutes for Diabetic Patients.**—WILLIAMSON (*British Med. Jour.*, 1917, 2921, 870) gives formulas for home-made bread substitutes which have been of great service to him in his care of diabetic patients. The following formula is a sample upon which a number of different combinations are based. Formula: Soluble casein, 3 tablespoonfuls; gluten flour, 2 tablespoonfuls; baking powder, ½ teaspoonful; 1 egg well beaten; small pinch of salt. Mix well together, adding the baking powder last. A little water may be added if necessary. Drop into six tins and bake twenty minutes. Formulas are also given for various combinations of the soluble casein with cocoanut powder and almond flour with and without gluten. He advises that diabetic patients should not try one bread substitute only but they should try several until the most palatable is obtained for the individual patient.

## PEDIATRICS

UNDER THE CHARGE OF

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**Communicability of Poliomyelitis.**—KERLEY (*Arch. Pediat.*, 1917, xxxiv, 32) offers interesting observations bearing on the questions of the transmissibility of the disease by the diseased to the unprotected individual by human contact; the part played by the innocent in the transmission of the disease, and the proportion of healthy children who are susceptible. The following facts have a striking relation to transmission by human contact: There were no cases of the disease on Governor's Island, New York, during the recent epidemic. There are about 80 children on the island, and a strict quarantine of children under sixteen years was maintained throughout the epidemic. There were no cases on Barren Island, with 350 children, in a population of 1500 people. The geographical and social isolation of this community can be considered responsible for its immunity from the disease. Among the 21,746 children in 93 institutions under permanent jurisdiction of the Health Department of New York City, but 10 proved cases developed. Three of these developed within two weeks of their admission to the institutions and three others were allowed to mingle with city children in a public park. This low morbidity is to be ascribed to the strict quarantine established in these institutions by the Department of Health. The conclusion being safe that the disease would spread along the lines of human travel to isolated sections, the author thoroughly investigated a number of first cases occurring in isolated communities in northwestern Connecticut, in which the disease had not been known to exist for a period of ten years. He reports 11 cases of the disease under the above conditions, and in almost all the cases it was proved that some person coming from an infected locality had come in contact with the case just previous to its development, the infection being borne by the innocent carriers. In 2 cases the disease was transmitted by coming in personal contact with children recently arrived from an infected locality who were at the time or quite recently ill from a condition not diagnosed as poliomyelitis but which was later shown to have been that disease in its abortive form. The author concludes as reasonable that poliomyelitis may be communicated through personal contact and that there are innocent carriers who spread the disease. Also, that but a small percentage of children are susceptible to the disease and that probably from 90 to 95 per cent. possess an immunity.

**Some Clinical Aspects of Anterior Poliomyelitis.**—MARTIN (*Canadian Med. Assn. Jour.*, 1917, vii, 113) states that recent observations and researches of this disease demonstrate the need of reconstructing our ideas of it. Epidemics show that even the very large

proportion of the cases are not accompanied by paralysis. The disease appears to affect all ages and classes. It is essentially infectious and communicable, the virus apparently entering the body through the mucous membranes of the nose, throat, and intestines, and affects chiefly the nervous system. The mode of infection is undoubtedly by personal contact, and convincing evidence has demonstrated that no intermediate way exists. Flies and domestic animals do not communicate the disease except as passive carriers. Healthy, contaminated persons can carry the virus through the secretions of their mucous membrane. Many people have a natural immunity to the disease. The average incubation period is eight days. The prodromal stage if present shows indefinite body pains, fatigue and pressure or aching of the head. The onset shows a high fever of short duration and usually ending by lysis. The general symptoms are headache, vomiting, constipation, pains generally over the body but particularly in the nape of the neck. Stiffness of the head and neck, refusal to flex the chin on the breast. Hyperesthesia is characteristic and, as a rule, diffuse. Weakness, with flaccidity of the muscles, and drowsiness are characteristic symptoms. These symptoms may last from five to ten days followed by rapid recovery, when the case is termed "abortive." However, recurrence may follow with a subsequent paralysis. The various types of the disease are described, depending on the anatomical lesion in the nervous system. The abortive type comprises 35 to 56 per cent. of all cases, and is the most dangerous form from the point of dissemination of the disease. During epidemics every person with an acute infection is rightly to be regarded as a suspect.

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**Early Diagnosis of Pott's Disease.**—TAYLOR and DARLING (*New York State Jour. Med.*, 1917, xvii, 51) impress the value of habitually thorough examination of children in illness in avoiding errors in diagnosis of this disease. Pott's disease is essentially a disease of childhood, 90 per cent. of cases occurring before the fifteenth year. It is desirable, if possible, to make a diagnosis before destruction of vertebræ or surface abscess formation occur. The disease develops more rapidly in children than in adults and abscess or deformity may appear in a few months. Among the earliest signs of the disease in childhood are general debility, slight anemia, failure to gain, lack of interest in play, tendency to lie down often, unnatural attitude, change in gait, night cries or paroxysmal abdominal pain or persistent attacks of pain in the chest or stomach. The child moves cautiously, leans on a table or chair at every opportunity and tends to walk on toes. These symptoms are suspicious. On inspecting the spine, if the lesion is cervical there may be unnatural posture of the head or supporting the chin with the hands when sitting. The most usual location of the lesion in children is the dorsal region and with this situation may be found elevation of one or both shoulders, rigidity of the spine when walking and placing the hands on the thighs to support the spine when sitting. A slight lateral curve may be seen. If the disease is lumbar there is exaggeration of the normal curve which throws the abdomen forward and the child characteristically squats instead of stooping to pick up an object. It may be possible to detect approximation of two vertebra

when the spine bends or interruption of the normal curve of the spine when the child leans forward. Waterman and Yager in an analysis of 1000 cases found the most frequent early signs in young children to be the unnatural attitude and the pain and muscular rigidity.

## GYNECOLOGY

UNDER THE CHARGE OF

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**Radium Treatment of Cervical Carcinoma.** — Reports upon this subject are now becoming quite common in the American literature, showing that numerous clinics are giving it a trial, and while these reports for the most part are as yet distinctly preliminary in nature, and cover small series of cases, they are of interest in showing the development of the technic and applicability of the treatment. In a recent report FRANK (*Jour. Cancer Research*, 1917, ii, 85) says that he has had put at his disposal 130 mgs. of radium, contained in four tubes, the largest holding about 80 mgs., and the others smaller amounts. For the treatment of small carcinomata, where concentration of the rays is desirable, he has devised a hollow lead cup on the end of a long handle of stiff wire. The uncovered glass tubes, containing the radium, are put in this cup, which is then closed with a brass lid held in place by adhesive, and the whole covered by a small rubber bag 1 mm. in thickness to cut out the secondary rays. Thus all the rays are blocked in all directions but in the one in which it is desired to have them act. For larger cauliflower growths, the chief radium tube is placed in a brass capsule 1.5 mm. thick, which is screwed to the end of a long wire handle. If a larger dosage than this affords is desired, the additional tubes are fastened around the periphery of the first with adhesive, and the whole then covered with a rubber bag and introduced together by means of the handle. In crater-like carcinomata the central tube is advanced a couple of centimeters ahead of the three smaller ones, thus permitting its introduction into the cervix, the smaller tubes at the same time radiating the vaginal portion and fornices. If it is desired to screen one side, this is done by introducing four to eight thicknesses of lead foil inside the rubber bag. Unless the carrier is to be introduced actually inside the cervical canal a layer of gauze is interposed between it and the growth. The carrier is always introduced by sight after retraction of the vaginal walls; it is pushed firmly against the gauze by means of the handle, and the vagina is then tightly packed with gauze so that its walls are separated as far as possible from the radium. The handle remains sticking out of the vagina, and is secured to the vulva by means of strips of adhesive. The radium is usually allowed to remain in place eighteen to twenty-four hours; the frequency of

application depends largely upon the reaction (pain, rectal and vesical tenesmus, symptoms of absorption or toxemia). The usual routine followed by the author is to give a second treatment seven to ten days after the first, and if improvement is apparent two more at intervals of three weeks with diminishing dosage, applying in this first series a total of 5000 to 6000 milligram hours. Thereafter one treatment each month completes the primary treatment; the patient presents herself at least once a month, and if a recurrence manifests itself a new series of radiations is undertaken. Frank has followed most of his cases by the microscopic study of excised bits of tissue from time to time, and has found the usual cell changes that have been often described. The limit of penetration of direct action of the radium appears to be about 1.5 cm., but the author believes that cancer cells may be destroyed beyond this zone by the strangling action of the contracting connective tissue, which is greatly stimulated by the radioactivity. In one instance, a uterus the seat of a well developed squamous carcinoma of the cervix was removed by radical operation seven weeks after the beginning of treatment and cut in serial sections, but only two very small suspicious areas of malignancy could be discovered. In common with all other careful observers, however, Frank warns against forming false hopes of permanent cures in these cases, and considers that all we can say of radium at present is that it is the best palliative—though only a palliative—treatment for inoperable cases of cervical cancer.

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**Significance of Hematuria.**—An interesting analysis of 238 cases of hematuria has been made by KRETSCHMER (*Jour. Am. Med. Assn.*, 1917, lxviii, 598), who very properly calls attention to the great importance of this symptom, since with very few exceptions it means organic disease in the urinary tract, and yet it is very often disregarded and belittled by both patient and physician. It is often unaccompanied by pain, and as the exact location of the trouble is usually difficult of determination, various styptic drugs are administered, while both patient and physician *wait* for the bleeding to stop. The fact that a large percentage of these cases are in reality due to new growths or tuberculosis of the kidney, conditions in which early treatment is of vital importance, should indicate the necessity for making an early, accurate diagnosis. Of the 238 cases studied by Kretschmer, an accurate diagnosis was made in 197. In 74 of these the trouble was in the kidney, the list of lesions being headed by tuberculosis and nephritis, with 23 and 12 cases respectively. Next in order of frequency came renal calculus, hypernephroma, and colon-bacillus infection, with 8 cases each, then carcinoma, other renal tumors, polycystic disease, trauma, and hydronephrosis, with 2 cases each. Pyonephrosis, movable kidney, pregnancy, doubtful stone, and oxaluria each accounted for a single case. The bladder was the seat of the hemorrhage more often than the kidney, being involved 86 times. The largest number of these cases, 36, were due to carcinoma; papilloma was responsible 26 times, calculus 14 times, and vesical tuberculosis 10 times. There were two cases of diverticula, and one each of angioma and polypi. The prostate was the source of the hemorrhage in 25 cases in males, ureteral calculus was the factor 10 times, and prolapse and tumor of the female urethra once each. Taking the series as a whole, tumor formation in some portion

of the urinary tract was distinctly the most frequent cause of hemorrhage, followed by tuberculosis and calculus. In many of these cases, it was necessary to study the patients over considerable periods of time, and to make numerous and varied examinations, before the true condition was determined. Kretschmer says that he makes it a rule to inject guinea-pigs routinely in all cases of obscure hematuria, as it is at times impossible to demonstrate tubercle bacilli in the sediment of urine containing a large amount of blood. In the remaining cases of the series, the source of the hemorrhage but not its cause was determined in about a third. Most of those in whom neither the origin nor the cause could be determined either refused instrumental examination, or for some reason this could not be carried out. In only 6 cases of the entire series in which complete examinations were made was no light thrown on the condition. In these, cystoscopic examination, ureteral catheterization, cultures of the urine, roentgen-ray examination and pyelography were all completely negative. The author does not consider these cases of so-called "essential hematuria," but merely expressions of our present diagnostic limitations, and thinks they should be subjected to further clinical observation.

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**Gangrene of the Uterus following Criminal Abortion.**—MAUCLAIRE (*Ann. de gynéco. et d'obst.*, 1916, xlii, 193) calls attention to the fact that serious and often fatal symptoms may arise following the introduction of irritating solutions or unclean instruments into the uterus due to gangrene of the wall of the fundus, associated with a small area of perforation, or even in the absence of any perforation. He cites 4 cases, in 2 of which no perforation has occurred primarily, though in one of these a large perforation in the fundus, due to gangrene, was found in the uterus removed at autopsy twelve days after an exploratory operation, at which the peritoneal covering of the uterus was found to be intact, with a recognized subperitoneal area of beginning gangrene, the uterus, however, not being removed at that time. In the second case, two spots of subperitoneal gangrene, at the tubal angles, with intact peritoneum, were recognized at operation and the uterus removed; microscopic examination verified the diagnosis. In all these instances, the gangrenous area is more or less conical in shape, with the apex in, corresponding in outline to that of an infarct, a condition that is explained by the anatomical relationships of the terminal vessels in the fundus. Leclerc and Crispin have shown by injection experiments that in the fundal region the terminal arteries approach the intertubal line without anastomoses, differing in this respect from the vascular arrangement in the corpus and cervix. The fundus is therefore in a poor condition for defense against vascular lesions, and an infection in the uterus causing thrombosis of one of these little terminal arterioles may easily lead to the formation of a gangrenous perforation even though no actual mechanical perforation was caused at the time of the instrumentation. This fact emphasizes, in Mauclaire's opinion, the necessity for the most careful watching of these cases, and the performance of an immediate laparotomy upon the first vestige of peritoneal symptoms, even if it appears exceedingly unlikely that the preceding manipulations had actually resulted in perforation of the uterine wall.

# OBSTETRICS

UNDER THE CHARGE OF

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**Ophthalmia Neonatorum.**—The frequency and prevention of this disorder are considered in the public health report of the city of London, on which an abstract is made in the *British Med. Jour.*, September 16, 1916. 537 cases during a year were investigated, of which 456 completely recovered. In 6 there was permanent impairment of vision, in 1, definite history of gonorrhea in both parents, and both eyes of the child were affected from the moment of birth. Instructions were given to take the child to the hospital for treatment, but this was not done, and the child became blind in both eyes. Among the mothers there was a history of vaginal discharge in over one-third of the cases, 39.6 per cent. Among the children having ophthalmia 20 died while suffering from the disease. In 53 cases the parents took the child from observation before a definite termination of the case had occurred.

**Lumbar Puncture in the Fetus.**—COSTA (*Jour. Ann. di Ostet.*, No. 6, 1916) discusses the problem of lumbar puncture upon the fetus in cases of breech presentation where birth is difficult because of contracted pelvis in the mother, or excessive development in the child. He described a case of contracted pelvis with a conjugate avara 7.4 cm. in which lumbar puncture was done upon the fetus in breech presentation, resulting in the spontaneous expulsion of a female child weighing 3200 gm. and 50 cm. in length. The fetus died on the fourth day after birth from general debility, and a careful examination failed to disclose any injury to the nervous system resulting from the lumbar puncture. Other similar cases are cited, and the conclusion of the writer is that this method has a distinct field of usefulness, especially in cases in which there is moderate pelvic contraction.

**Rupture of the Scar of a Previous Cesarean Section.**—FINDLEY (*Am. Jour. Obst.*, September, 1916) has collected 63 cases in which rupture of the uterine scar has occurred in patients upon whom previously Cesarean section had been performed. The analysis of these cases shows that a perfectly healed scar may be relied upon to resist the force of labor, but as one cannot tell what happens to the Cesarean wound after operation in most cases, every precaution must be taken to secure accurate and aseptic union. The principles of suture produced by Sänger which call for the accurate closure of the uterus muscle separately, followed by closure of the peritoneal covering of the uterus, must be strictly followed. A second important factor is absence of infection. There may be present a latent gonorrheal infection which may defeat the most careful efforts to secure a perfect healing. When after Cesarean section the patient's convalescence has been complicated

by fever, this must be regarded as a sign that the wound in the uterus is not properly healed, and should such a patient come into subsequent labor, she should be delivered by section at the onset of labor. In all cases of labor where infection is known to exist, and the necessity for section arises, sterility and hysterectomy should be performed, and not the ordinary conservative section. Transverse, fundal, extraperitoneal and cervical incisions have not lessened the liability of rupture in the uterine scar, but have probably increased it. In cases of Cesarean section the danger of subsequent rupture of the scar is not so great that each Cesarean section should be followed by sterility. Patients who have had section and who subsequently become pregnant should be delivered in a hospital with skilled attendance where operation could be promptly performed if necessary. Version, high forceps, tamponing the uterus, the use of bags, and the giving of pituitrin should never be employed in patients who have a Cesarean scar. Not more than 2 per cent. of cases delivered by section have a rupture of the scar in subsequent labor, and this shows that the argument "once a Cesarean section always a Cesarean section" is not reasonable. There is, however, sufficient danger to forbid the indiscriminate use of the Cesarean operation.

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**A Practical Method of Estimating the Condition of the Ovaries.**—In an article upon fertility and sterility, REYNOLDS (*Jour. Am. Med. Assn.*, October 21, 1916) draws attention to the fact that at operation practical idea of the condition of the ovaries may be obtained by a careful palpation. The consistence of the normal ovary is distinctly soft and elastic and uniform. One of the most frequent pathological processes found in the ovaries is sclerosis, and this can be appreciated better by touch than even by sight. The decision to remove or leave an ovary in a given case may often be properly made by careful palpation of the ovary, and the recognition of a considerable area which is normal in consistence. Where, on the other hand, nothing but firm sclerotic tissue is present the ovary is in all probability incapable of function.

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**Rupture of the Uterus following the Use of Pituitrin.**—MCNEILE (*Am. Jour. Obst.*, September, 1916) reports the case of a strong-looking Mexican woman who had three labors previously, two terminated by the use of forceps and one spontaneously. The position and presentation in the fourth labor were normal and favorable, and as uterine contractions grew feeble during labor, pituitrin was given. This was immediately followed by tetanus of the uterus with pain in the epigastric region and chest. Uterine contractions ceased. Later the patient was delivered of a stillborn child. Hemorrhage followed and when the hand was introduced into the uterus to deliver the placenta it was found in the abdominal cavity. On admission to the hospital the patient was semicomatose, and on section a transverse rupture of the lower segment was found, the edges of the tear badly lacerated. A supravaginal hysterectomy was done with drainage; the patient recovered. On subsequent examination the pelvis was obliquely contracted. In the literature including his own, the writer has collected 16 cases of rupture of the uterus following the use of pituitrin, with thirteen deaths. After considerable experience with the drug the con-

clusion is that pituitrin has absolutely no place in normal obstetrics, and in selected cases only, under accurate observation and skilful care, is its use permissible. The reviewer has recently seen a case where separation of the placenta followed the administration of pituitrin; also a case of contracted pelvis where pituitrin was given repeatedly, and forceps used unsuccessfully, and a case of uterine rupture following the use of pituitrin. This substance is probably the most dangerous drug at present in the hands of the general profession.

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**Spontaneous Rupture of the Uterus.**—TELFAIR (*Am. Jour. Obst.*, September, 1916) reports the case of a patient admitted to hospital in shock, with breech presentation in which the fetus could not be safely delivered by traction. On opening the abdomen a transverse rupture across the vaginal vault was found opening up the broad ligament on the left side and extending up upon the uterus. Craniotomy and extraction were immediately performed followed by hysterectomy. The patient did not survive the operation. In discussion a case was described in which after a perfectly normal and rapid labor a patient had died from profuse hemorrhage behind the peritoneum arising from a tear in the left broad ligament which had opened the uterine artery. It also developed in discussion that a spontaneous rupture of the uterus can occur as low as the broad ligaments without interference during labor.

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**Pregnancy following Extensive Operations upon the Pelvic Organs.**—VINEBERG reports a case where a gangrenous appendix was removed, also one tube and ovary, and adhesions around the other tube freed, and the opening of the closed tube resulted, the ovary remaining. Although the operation was a difficult and extensive one, the patient made a good recovery and subsequently became pregnant. Speaking from clinical experience there seems to be no condition in the abdomen so complicated by adhesions that pregnancy may not occur if ovarian tissue be left and one tube which is in any degree patent.

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**The Transmission of Hereditary Syphilis.**—GAUCHER (*Bull. de l'Acad. de méd.*, September 26, 1916) reports the case of an apparently healthy young couple free from acquired venereal disease who had three children presenting the manifestations of inherited syphilis of a severe type. One child is an idiot. Gaucher had been the physician of the grandfather, and remembered that although this man had never acquired venereal disease, that he had hereditary syphilis. He died in early manhood from syphilitic paraplegia. This interesting case illustrates the potency of hereditary syphilis even to the fourth generation.

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**Puerperal Eclampsia.**—SCHEULT (*Jour. Obst. and Gynec. Brit. Emp.*, June–August, 1915) gives the results of his operations on 122 cases of puerperal eclampsia in the hospital at Trinidad. His observations show that in the majority of cases nephritis was present in varying degree. The greater number of these cases were primiparæ and the influence of twin pregnancy is recognized in causing eclampsia. The disease seemed less frequent when the weather was driest and the coming of the rainy season was followed by an increase in the number of cases. The maternal mortality was 22.9 per cent. and the fetal mor-

tality was 34 per cent. Three cases after recovery had marked mental disturbance and had to be treated in asylums. Four patients recovered from eclampsia without coming into labor, three of whom went to full term and one was delivered prematurely. In one case a full term, well-developed child developed eclampsia convulsions seventeen hours after birth, which proved fatal.

## OTOLOGY

UNDER THE CHARGE OF

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**The Pathology of Otosclerosis.**—By J. S. FRASER and R. MUIR (*Jour. Laryngol., Rhinol., and Otol.*, vol. xxxi, No. 11).—This communication, a part of the report for the year 1915 from the ear and throat departments of the Royal Infirmary at Edinburgh, is a valuable contribution to the record of the pathological facts and an inferential study of the etiology of the several forms of tissue change in the middle ear or labyrinth, which have been grossly included under the title name of this communication, and includes various references to the literature of the subject and suggested explanations of the concomitant symptoms, the paper moreover being richly illustrated by plates of microscopic sections. The theories as to the pathology of otosclerosis fall under four headings: That it may be congenital; that it may follow inflammatory changes in the middle ear; that it may be due to infection through the blood; and that it may be caused by abnormal conditions in the nerve supply of the parts affected. (1) According to the first theory, otosclerosis is a congenital anomaly of the process of growth in the petrous portion of the temporal bone, due to the presence of certain determinants in the patient's blood. This anomaly only becomes manifest after puberty. (2) Otosclerosis is regarded by some as a chronic inflammatory process spreading from the mucoperiosteum of the middle ear and following attacks of catarrhal or suppurative otitis media. The inflammatory condition is supposed to linger about the niche of the oval window and to invade the bone from the deep layer of the mucosa. Such an invasion may be favored by the anastomosis which occurs at this spot between the tympanic vessels and those of the bony labyrinth capsule. Further, as has been pointed out, the joints in the middle ear are the only articulations in the body covered by mucous membrane, and therefore liable to infection from the surface. (3) A third group of otologists look on otosclerosis as a primary disease of the bone, the infection coming by the way of the blood-stream, as in osteomalacia, rheumatism, etc. Ferreri regards otosclerosis as closely allied to osteomalacia, and finds that almost all patients suffering from the latter disease are also the subjects of otosclerosis. A variant of this view is held by A. A. Gray, who has put forward the theory that otosclerosis is an aseptic

necrosis of certain areas in the labyrinth capsule—apparently as a result of aseptic infarction. Gray believes that similar areas occur in other bones of the skeleton. (4) Lastly otosclerosis is regarded by a small group of observers as due to a trophic disturbance—*i. e.*, as a degenerative atrophic process. According to this theory the changes (sometimes) found in the ganglia and nerves are primary, while those in the labyrinth capsule are secondary. In this connection it may be noted that certain cases, which clinically appeared to be examples of *nerve deafness*, on microscopic examination showed spongification of the labyrinth capsule with (Siebenmann) or without (Bruehl) ankylosis of the stapes. This type of otosclerosis associated with nerve deafness—the so-called "atypical otosclerosis"—is markedly hereditary. The author of the second part of the paper gives a compact statement of the pathologic changes as determined under section and microscopic observation, and points to the fact that the study of sections from cases of otosclerosis strongly suggests the structural changes met with in other bony tissues in conditions of chronic toxemia or altered metabolism. Whatever be the exciting cause of this condition we have a series of progressive changes which appear to be *purely inflammatory* in character. The ultimate result is a typical and constant lesion, viz. marked sclerosis of the bony tissue of the labyrinth capsule. The alleged absence of plasma cells does not prove that otosclerosis is of non-inflammatory origin. These cells are not present in all forms of chronic inflammation. Even when they are present they do not occur in all stages of the inflammatory process. For their detection special staining methods are required—methods difficult to apply to celloidin sections of the labyrinth. The first change one observes in otosclerosis is the marked and general engorgement of the bloodvessels both in the fatty marrow of the bone and in the mucoperiosteum. The connective tissue of these areas is also seen to increase in amount, having a loose, open, and fibrillated structure. There are more cellular areas, mainly composed of mononuclear cells, which are closely related to the congested vessels. Some of the medullary spaces in the petrous bone show leukoblastic marrow reaction. Such appearances can be explained by a toxic body brought by the blood or stimulant, especially on the connective tissues of the marrow. The condition is essentially a granulating process, which slowly brings about absorption of the bone, allowing the opening up of the medullary spaces. The deeply staining bone seen around the enlarged medullary spaces appears to be old bone which is undergoing change, and not new-formed bone, as described by various writers. The granulation tissue tends to become more fully formed fibrous tissue, and these fibers range themselves in concentric layers around the central vessel. Ossification of this fibrous tissue now sets in, beginning with the fibers lying in close relation to the bone trabeculæ, thus bringing about a marked thickening of the lamellæ at the expense of the Haversian canals. The inner layer of the bone in the labyrinth capsule also appears to be involved in this process of sclerosis. There is an active proliferation of the cartilage cells and ossification into a bony matrix.

The above changes seem to be of a patchy character and appear to begin at the junction of the cartilaginous and lamellar portions of the labyrinth capsule, and to spread directly along that line for some distance, extending more or less into the cartilaginous and lamellar bone

on each side, and in places passing right through the cartilage bone to reach the endosteal tissue lining the cavities of the inner ear. This path of extension strongly suggests some direct channel, such as that shown to exist, and would explain the areas of change seen in the various parts of the labyrinth capsule. The whole process appears to be a slow form of inflammation, a definite series of reactions of a special tissue to repair damage caused by some unknown element, bacterial or toxic. As a result of their investigations the authors arrive at the following conclusions. (1) Some cases of otosclerosis (spongification of the labyrinth capsule) appear to be of the nature of a blood infection, and may be called "primary." We would expect that further research would show that in these cases the bony changes are widespread throughout the skeleton. (2) Other cases of otosclerosis undoubtedly follow attacks of catarrhal or purulent otitis media, the infective process invading the labyrinth capsule at the anterior margin of the oval window. Such cases may be called "secondary." (3) From the clinical stand-point, heredity plays an important part in otosclerosis, but, as the condition is a chronic inflammatory process, the infective agent must gain access to the labyrinth capsule either through the blood-stream or from the middle-ear cleft. (4) It has been proved by clinical and microscopic research that "atypical" cases of otosclerosis exist in which functional examination of the ear reveals the presence of nerve deafness. The relationship between the bony changes and the nervous affection is not yet clear.

## HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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**The Minimum Number of Bacilli Required to Transmit Tuberculosis to Guinea-pigs.**—I. THÖNI and A. C. THAYSEN (*Zentralbl. f. Bakteriol.*, 1916, Part 1, p. 308) report the following: The dose of injection was standardized by Burri's method, which permits an accurate count of the bacteria. In the first series of experiments 19 guinea-pigs were injected with a highly pathogenic culture, the individual doses of which contained between 10 to 76 tubercle bacilli. Only one pig, the one which had been injected with 71 bacilli and which died after forty-one days with symptoms of dysentery, showed signs of tuberculosis. In a second series of experiments 3 strains of the bacillus, two of which were highly virulent, were employed. Twenty-two guinea-pigs received doses containing between 99 and 343 bacilli. No tuberculosis developed.

These results are at variance with the ones obtained heretofore. Previous experiments of others seemed to have shown that one or few (10 to 20) bacilli are sufficient to convey tuberculosis. The author believes that the previous experiments are erroneous. He believes that the methods employed to standardize the bacterial emulsion did not permit a high degree of accuracy.

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**The Comparative Resistance of Bacteria and Human Tissue Cells to Certain Common Antiseptics.**—LAMBERT (*Jour. Exp. Med.*, December 1, 1916, xxiv, No. 6) found that the comparative resistance of bacteria and human tissue cells to antiseptics and other chemicals may be easily tested by tissue cultures under conditions which approximate those found in the living body. A comparative study shows that while human cells (connective tissue and wandering cells) are highly resistant to many antiseptics, they are in general more easily killed than bacteria (Staphylococcus aureus). Of the antiseptics tested, which include mercuric chloride, iodine, potassium mercuric iodide, phenol, tricresol, hydrogen peroxide, hypochlorites (Dakin's solution), argyrol, and alcohol, the one which approaches most closely the ideal disinfectant is iodine, which kills bacteria in strengths that do not seriously injure connective-tissue cells or wandering cells.

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**Anaphylactic Shock in Dogs.**—J. P. SIMONDS (*Jour. Infect. Dis.*, December, 1916, xix, No. 6) concludes that anaphylactic shock in the dog is associated with a fall in blood-pressure. During the period of low pressure the reaction to injections of epinephrin is either absent or greatly diminished, while the response to nicotin may be augmented. It is believed that the mechanism of the latter is chiefly dependent on its effect on respiration, and only to a very limited extent or not at all on direct stimulation of the vasomotor center or the sympathetic ganglia. There is evidence for the belief that there is present a condition of decreased irritability of the sympathetic ganglia and possibly of the vasomotor center. The prompt rise in arterial pressure after injections of nicotin associated with dyspnea is evidence that in anaphylactic shock in the dog there is no constriction of the vessels of the lungs.

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**Destroying Lice on Typhus Fever Suspects.**—S. R. GRUBBS (*Public Health Reports*, October 20, 1916, xxxi, No. 42) states that in excluding typhus fever from the United States it is important to have some efficient and rapid method of killing lice on the human body. As a result of studies made at the Boston quarantine station, the United States Public Health Service has adopted a method of treating persons with a gasoline soap spray and shower bath and of treating clothing and baggage with a vacuum hydrocyanic acid gas process. The formula for the gasoline soap is as follows: Soap chips or laundry soap, 1 part; soft water, 4 parts; gasoline, 4 parts. The soap is dissolved by boiling in the water and the gasoline is added after removing from the fire. This mixture hardens to a jelly and for spraying, 1 part of this is mixed with 5 to 10 parts of hot water. Each person is sprayed thoroughly from head to foot with the gasoline soap solution and then compelled to walk through a shower tank 15 feet long, 10 feet of this under the shower which washes off the soap. For the treatment of lousy clothing

and baggage different methods have been tried but the treatment with cyanide seems to be the most advantageous. The method of cyaniding is that used to cyanide cotton bales to kill the pink ball worm, and consists of creating a vacuum in a metal chamber holding the articles to be disinfected, liberating cyanide gas in the chamber and allowing air to enter which forces the gas into the articles. Experiments performed to decide the length of time and the amount of vacuum necessary to thoroughly disinfect tight packages of various kinds showed that lice in ordinary hand-baggage will be killed by the vacuum-cyanide method with fifteen in vacuum and 30 minutes' exposure to hydrocyanic acid gas from four ounces of Na C.N. per 100 cubic feet. If trunks are to be treated by this method, the lids should be opened. After disinfection clothing and baggage are returned to the owner free from vermin; but otherwise in an unchanged condition. The method of generating the cyanide is simple and inexpensive, and the generator may be attached to any steam chamber while for the vacuum an electric or gasoline driven air-pump will work rapidly and successfully. Hydrocyanic gas has very slight power to kill bacteria and should not be used for this purpose.

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**Experiments on the Destruction of Body Lice.**—FRIEDMAN (*Zentralbl. f. Bakteriol.*, 1916, Part 1, p. 320) carried on laboratory experiments with the view of reproducing actual conditions. The lice were packed into several layers of woollen, silk and other fabric and then exposed to various destructive agents. Live steam killed the parasite and the eggs within five minutes. In the municipal steam disinfection operators it required three hours' exposure to obtain a similar result (three larvæ developed subsequently in the exposed material). A ten-minute exposure to dry air of 70° C. is very efficient. Five commercial powders (trade name not given) were examined and found to be of no insecticidal value. Further experiment showed that lice will eagerly look for woollen fabric and that they will shun silk. They will deposit eggs on wool and none on silk if they have their choice. The development of larvæ on silk is very much delayed. An exposure of lice to carbon disulphide at 12° C. for twenty-four hours in a closed bottle proved very effective. The fumes penetrated five layers of wool and other material. The smallest quantity of carbon disulphide required for efficient work was 54 to 57 mg. per liter of air and a six-hour exposure. With sulphur dioxide 100 mg. of the gas per liter of air and four to five hours' exposure seemed necessary to kill the parasite. Sulphur dioxide is a very destructive gas and carbon disulphide is to be preferred.

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**Experiments on the Immunization against Louse Bites.**—GALLI-VALERIO (*Zentralbl. f. Bakteriol.*, 1916, Part 1, p. 262) experimented on his own person, rubbing at various times 40 different substances on his forearm and placing P. cervicalis within, on the edge, near the medicated area. He permitted these lice to bite him, making observations on the frequency of bites. Not one of the substances, most of which were essential oils, proved to be of positive immunizing value.

# PATHOLOGY AND BACTERIOLOGY

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**The Relation of the Bronchisepticin Skin Reaction to Immunity in Canine Distemper Including the Bactericidal Action of the Dog Serum for B. Bronchisepticus.**—KOLMER, MATSUNAMI and HARKINS (*Jour. Immunol.*, 1916, i, 571) cite some very interesting experiments in which they endeavored to discover some relation between the bronchisepticin skin reaction and the immunity of dogs to distemper. In a previous article in the same journal, Kolmer, Harkins and Reichel described the preparation of bronchisepticin, their technic in using it as well as some results which were obtained in animals inoculated with this antigen. In the previous experiments the results indicated that there was little or no relation between immunity to distemper and the bronchisepticin skin reaction, though experimentally the reaction did have some diagnostic value. The experiments cited in the present communication are more complete and they confirm the previous conclusions. The present work included observations on the agglutination, bacteriolysis and complement-fixation tests on the sera of dogs having the disease at the time of the experiments, of dogs which had recovered from the disease and of dogs which had been vaccinated with an emulsion of dead bronchisepticus organisms. The tests were all carefully controlled and the readings of the results were very interesting but in all they tended only to prove that the relation of this skin reaction to immunity from Bacillus bronchisepticus is practically "nil." The authors emphasize, however, that even though this last be true the test has a diagnostic value in that a very high percentage of positive reactions is obtained in dogs having distemper and also in dogs which have recovered from this disease.

**The Relation between the Thyroid and Parathyroid Glands.**—In a recent study, TANBERG (*Jour. Exper. Med.*, 1916, xxiv, 547) has brought forward some evidence to show that the accepted views on the functional coöperation between the thyroid and parathyroid gland may require readjustment. In a previous paper, this writer had demonstrated that in rats an excessive meat diet produces hypertrophy of the thyroid appearing in the gross as an increase in size and weight, and microscopically as a proliferation of the epithelial elements, with at the same time a loss of the colloid substance. In the present work,

cats are used. The same results were obtained in these animals when kept on a diet consisting entirely of meat and water. However, it was noted that if insufficiency of the parathyroids was induced in meat-fed animals by the extirpation of two or more of these small glands, the usual hypertrophic picture did not develop in the thyroid. It was found, too, that the hypertrophy of the thyroid induced by a meat diet disappeared after excision of a sufficient number of parathyroids. In one instance, the animal lived, though a chronic tetany developed, after excision of four (microscopically demonstrated) parathyroids. In it, tetany was accompanied by a rapid decrease in size of the hypertrophic thyroid which had previously been developed in this animal by a meat diet. This unusual occurrence, in which an animal lived after excision of apparently all the parathyroid tissue was cleared up by the discovery of a fifth parathyroid when the animal was killed, more than a year after the first operation. Its thyroid was of normal appearance, though the animal had lived on a diet consisting solely of meat and water. Indeed, in chronic tetany, an atrophy rather than a hypertrophy of the gland is often developed, regardless of the diet. This evidence seems to point to some interrelation between the glands, at least to the extent that parathyroid insufficiency interferes with the function of the thyroid. Complete extirpation of the thyroid, however, produces little change in the gross and microscopic appearance of the parathyroids. Small tags of thyroid tissue which may be accidentally left during experimental thyroidectomy, take on a compact appearance, with small alveoli and scanty colloid; this hypertrophic picture may bear some resemblance to parathyroid tissue. In chronic tetany in which the remaining parathyroid tissue is insufficient, this tissue undergoes a curious hypertrophy, with the development of large transparent sharply defined cells having nuclei rich in chromatin. This picture differs from the hypertrophy of the parathyroids seen when the remaining glands are able, by this means, to compensate for parathyroid loss. In this latter condition, the remaining parathyroids assume a slight increase in size. The parenchymal cells definitely increase in size and uniformity of outline, though the increase does not approach that seen in chronic tetany. Animals with complete excision of the thyroid and the internal parathyroids, rapidly show symptoms of marked cachexia, but without evidence of tetany. These facts indicate that a decrease in parathyroid tissue may be compensated by that remaining, but that in the absence of the thyroid, none of its functions are undertaken by the parathyroids. Hence the author concludes that aside from the occurrence of direct or indirect interaction between the two glandular systems, the thyroid and parathyroids must be considered as independent organs each with specific functions, and that no proof of the existence of vicarious coöperation between the two has been established.

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